Organizacion CSA Ltda

CSA046966

PCT

OIL
RGC

Industria y Comercio

SUPERINTENDENCIA

"SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO"
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

09-82387

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: INHIBIDORES DE LA ACTIVIDAD DE Akt

SOLICITANTE: SMITHKLINE BEECHAM CORPORATION

DIRECCIÓN: One Franklin Plaza, P.O Box 7929, Philadelphia, PA 19101 E.U.A.

1/5

APODERADO: CARLOS R. OLARTE

BOGOTÁ 05 de Agosto de 2009

P2009/000140

OLARTERAISBECK
OLARTE RAISBECK MOURE

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-082387- -00000-0000
Fecha: 2009-08-06 17:19:24 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1095

Industria y Comercio
SUPERINTENDENCIA

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2009/000140**

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: SMITHKLINE BEECHAM CORPORATION
Dirección: One Franklin Plaza, PO Box 7929, Philadelphia, Pennsylvania 19101 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Estados Unidos de América.
Teléfono: _____ **Fax:** _____
E-mail: _____

IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE
Dirección: World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10
Teléfono: 601-7700 **Fax:** 601-7799
E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
C.C. [X] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual _____
Número 79782747Bta
TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA

(5)

PCT (86)

Solicitud Internacional No. PCT/US2008/053269 Fecha Febrero 7, 2008

Publicación Internacional No. WO 2008/098104 Fecha Agosto 14, 20078

(6)

Título (54) **INHIBIDORES DE LA ACTIVIDAD DE Akt**

Clasificación Internacional (51) A61K 31/12

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 7, 2007	60/888,586

(9)

Comprobante de pago No. 09- **Fecha** Agosto , 2009

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-02576
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

LISTA DE INVENTORES **PCT/US2008/053269**

1. **Mark Andrew SEEFELD,**
   1250 South Collegeville Road,
   Collegeville, PA 19426
   Estados Unidos
   Nacionalidad: Estadounidense

2. **Meagan B. ROUSE,**
   1250 South Collegeville Road,
   Collegeville, PA 19426
   Estados Unidos
   Nacionalidad: Estadounidense

3. **Dirk A. HEERDING,**
   1250 South Collegeville Road,
   Collegeville, PA 19426
   Estados Unidos
   Nacionalidad: Estadounidense

4. **Simon PEACE,**
   Gunnels Wood Road,
   Stevenage Hertfordshire
   SG1 2NY
   Gran Bretaña
   Nacionalidad: Britanica

5. **Dennis S. YAMASHITA,**
   1250 South Collegeville Road,
   Collegeville, PA 19426
   Estados Unidos
   Nacionalidad: Estadounidense

6. **Kenneth C. MCNULTY,**
   1250 South Collegeville Road,
   Collegeville, PA 19426
   Estados Unidos
   Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 09-082387- -00000-0000

Fecha: 2009-08-06 17:19:24 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1095

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 58,198
FECHA : AGOSTO 5 DE 2009

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	105799621	05/08/2009	3,402,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1	TRAMITES DE SOL. DE PATENTE DE IN	540,000.00
			TOTAL : $	540,000.00

SON: QUINIENTOS CUARENTA MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SMITHKLINE BEECHAM CORPORATION

PODER DE REPRESENTACION

Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario autorizado.

Certificado de Notario De Pinna en español certificando que Peter John Giddings es apoderado de Smithkline Beecham Corporation, firmado por James Kerr Milligan.

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
   - Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229470
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

Si el documento se usa en un país que no pertenece a la Convención de la Haya del 5 de octubre de 1961 debe pasar por la sección consular de la Misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Ingles
Resolución No. 2117 del 7 Oct 1987

DE PINNA
NOTARIES

Yo, el infrascrito, **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

C E R T I F I C O:

QUE es auténtica la firma "P. Giddings" suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la corporación denominada **"SMITHKLINE BEECHAM CORPORATION"**, corporación legalmente constituída y existente de acuerdo con las leyes del Estado de Pensilvania, Estados Unidos de América, con domicilio social en 1, Franklin Plaza, Philadelphia, Pensilvania 19101, Estados Unidos de América;

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debida y suficientemente autorizado para firmar documentos de esta clase, en virtud del Poder otorgado en su favor por la referida Sociedad fechado el 11 de julio de 2002, copia del cual he tenido a la vista.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy trece de agosto del año dos mil tres.

SCRIVENER NOTARIES

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra

DE PINNA
35 Piccadilly London W1J 0LJ
Telephone: +44 (0)20 7208 2900 Facsimile: +44 (0)20 7208 0068 DX No. 48521 Piccadilly 2

7

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by / a été signé par **James Kerr Milligan**

3. Acting in the capacity of / agissant en qualité de **Notary Public**

4. Bears the seal/stamp of / est revêtu du sceau/timbre de **The Said Notary Public**

5. at London/à Londres — Certified/Attesté

6. the/le **14 August 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs / par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G229470**

9. Stamp: / timbre:

10. Signature: **J. Garbrah**

FOREIGN AND COMMONWEALTH OFFICE LONDON

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
Fax: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

Poder

The undersigned,

El suscrito,

SmithKline Beecham Corporation

domiciled in

domiciliado en

One Franklin Plaza, P O Box 7929, Philadelphia, PA 19101, United States of America

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's **Patents, Utility Models and Industrial Designs** in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de **Patentes, Modelos de Utilidad y Diseños Industriales** de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised Official

Date/Fecha: 13 August 2003

City,Country/Ciudad,País: Brentford, Middlesex, England

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 August 2008 (14.08.2008)

PCT

(10) International Publication Number
WO 2008/098104 A1

(51) International Patent Classification:
A61K 31/12 (2006.01)

(21) International Application Number:
PCT/US2008/053269

(22) International Filing Date: 7 February 2008 (07.02.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/888,586 7 February 2007 (07.02.2007) US

(71) Applicant *(for all designated States except US)*: **SMITHKLINE BEECHAM CORPORATION** [US/US]; One Franklin Plaza, P.O. Box 7929, Philadelphia, PA 19101 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SEEFELD, Mark, Andrew** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **ROUSE, Meagan, B.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **HEERDING, Dirk, A.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **PEACE, Simon** [GB/GB]; Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **YAMASHITA, Dennis, S.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US). **MCNULTY, Kenneth, C.** [US/US]; 1250 South Collegeville Road, Collegeville, PA 19426 (US).

(74) Agents: **DUSTMAN, Wayne, J.** et al.; Glaxosmithkline, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.o. Box 1539, King Of Prussia, PA 19406-0939 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(54) Title: INHIBITORS OF AKT ACTIVITY

(57) Abstract: Invented are novel heterocyclic carboxamide compounds, the use of such compounds as inhibitors of protein kinase B activity and in the treatment of cancer and arthritis.

WO 2008/098104 A1

10

INHIBITORS OF Akt ACTIVITY

FIELD OF THE INVENTION

This invention relates to novel heterocyclic carboxamide compounds, the use of such compounds as inhibitors of protein kinase B (hereinafter PKB/Akt, PKB or Akt) activity and in the treatment of cancer and arthritis.

BACKGROUND OF THE INVENTION

The present invention relates to heterocyclic carboxamide containing compounds that are inhibitors of the activity of one or more of the isoforms of the serine/threonine kinase, Akt (also known as protein kinase B), suitably the compounds of the invention are inhibitors of the activity of all three isoforms of the serine/threonine kinase, Akt. The present invention also relates to pharmaceutical compositions comprising such compounds and methods of using the instant compounds in the treatment of cancer and arthritis (Liu et al. Current Opin. Pharmacology 3:317-22 (2003)).

Apoptosis (programmed cell death) plays essential roles in embryonic development and pathogenesis of various diseases, such as degenerative neuronal diseases, cardiovascular diseases and cancer. Recent work has led to the identification of various pro- and anti-apoptotic gene products that are involved in the regulation or execution of programmed cell death. Expression of anti-apoptotic genes, such as Bcl2 or Bcl-x_L, inhibits apoptotic cell death induced by various stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad, leads to programmed cell death (Adams et al. *Science,* 281:1322-1326 (1998)). The execution of programmed cell death is mediated by caspase -1 related proteinases, including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al. *Science,* 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Survival factors, such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I), promote cell survival under various conditions by inducing the activity of PI3K (Kulik et al. 1997, Hemmings 1997). Activated PI3K leads to the production of phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to, and promotes the activation of, the serine/ threonine kinase Akt, which contains a

pleckstrin homology (PH)-domain (Franke et al *Cell,* 81:727-736 (1995); Hemmings *Science,* 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999). It was demonstrated that Akt-2 was over-expressed in 12% of ovarian carcinomas and that amplification of Akt was especially frequent in 50% of undifferentiated tumors, suggestion that Akt may also be associated with tumor aggressiveness (Bellacosa, e*t al., Int. J. Cancer*, 64, pp. 280-285, 1995). Increased Akt1 kinase activity has been reported in breast, ovarian and prostate cancers (Sun *et al. Am. J. Pathol. 159:* 431-7 (2001)).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKBα, Akt2/PKBβ, and Akt3/PKBγ respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K

phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKBα occurs on two regulatory sites, Thr^{308} in the catalytic domain activation loop and on Ser^{473} near the carboxy terminus (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) and R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in Akt2/PKBβ and Akt3/PKBγ. The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3 '-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PdtIns(3,4,5)- P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the upstream kinase PDK1. The compound UCN-01 is a reported inhibitor of PDK1. *Biochem. J.* 375(2):255 (2003). Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams et al. *Curr. Biol.* 10:439-448 (2000).

Small molecule inhibitors of Akt are useful in the treatment of tumors, especially those with activated Akt (e.g. PTEN null tumors and tumors with ras mutations). PTEN is a critical negative regulator of Akt and its function is lost in many cancers, including breast and prostate carcinomas, glioblastomas, and several cancer syndromes including Bannayan-Zonana syndrome (Maehama, T. *et al. Annual Review of Biochemistry, 70*: 247 (2001)), Cowden disease (Parsons, R.;

Simpson, L. *Methods in Molecular Biology (Totowa, NJ, United States), 222 (Tumor Suppressor Genes, Volume 1)*: 147 (2003)), and Lhermitte-Duclos disease (Backman, S. *et al. Current Opinion in Neurobiology, 12(5)*: 516 (2002)). Akt3 is up-regulated in estrogen receptor-deficient breast cancers and androgen-independent prostate cancer cell lines and Akt2 is over-expressed in pancreatic and ovarian carcinomas. Akt1 is amplified in gastric cancers (Staal, *Proc. Natl. Acad. Sci.* USA *84*: 5034-7 (1987) and upregulated in breast cancers (Stal *et al. Breast Cancer Res. 5*: R37-R44 (2003)). Therefore a small molecule Akt inhibitor is expected to be useful for the treatment of these types of cancer as well as other types of cancer. Akt inhibitors are also useful in combination with further chemotherapeutic and anticancer agents.

It is an object of the instant invention to provide novel compounds that are inhibitors of Akt/PKB.

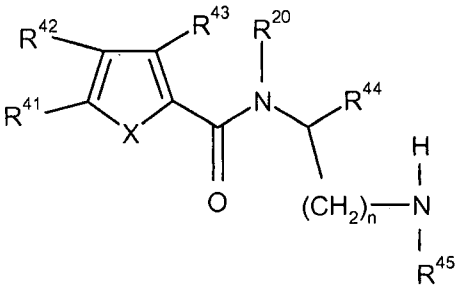
It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

It is also an object of the present invention to provide a method for treating cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

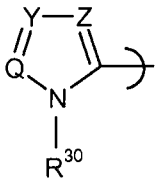
SUMMARY OF THE INVENTION

This invention relates to novel compounds of Formula (I):



(I)

wherein:



R^{41} and R^{42} are independently selected from: hydrogen, , halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan, substituted fruan, thiophene and substituted thiophene,

where Q and Y are independently selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and $-C(R^{48})-$, provided that at least one and at most 2 of Q, Y and Z are nitrogen, and R^{30} is selected from: C_{1-4}alkyl and C_{1-4}alkyl substituted with form one to three fluorine atoms,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cylcoalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan and thiophene;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAR$ wherein the AR is unsubstituted, $-(CR^{60}R^{61})_mAR$ wherein the AR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AR is a cyclic or polycyclic aromatic or saturated or unsaturated non-aromatic ring containing from 3 to 16 carbon atoms and optionally containing from one to three heteroatoms, provided that when the ring is aromatic and the number of carbon atoms is 3 the ring contains at least two

heteroatoms and when the ring is aromatic and the number of carbon atoms is 4 the ring contains at least one heteroatom, and R^{60} and R^{61} are independently selected from: hydrogen and C_{1-4}alkyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are C_{1-4}alkyl,

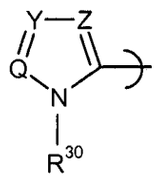
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, C_{1-4}alkyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and C_{1-4}alkyl; and

n is 0 to 2 and this moiety is optionally, if applicable, substituted by hydroxyC_{1-4}alkyl;

provided that one and only one of R^{41} and R^{42} is 

;

and/or pharmaceutically acceptable salts thereof.

This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

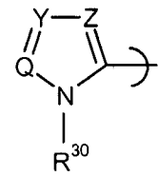
Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to compounds of Formula (I) as described above.

The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed herein inhibit each of the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those in which:



R^{41} and R^{42} are independently selected from: hydrogen, , halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan, substituted fruan, thiophene and substituted thiophene,

where Q is nitrogen, Y is selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and

$-C(R^{48})-$, provided that at most one of Y and Z are nitrogen, and

R^{30} is selected from: C_{1-4}alkyl and C_{1-4}alkyl substituted with form one to three fluorine atoms,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cylcoalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan and thiophene;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAR$ wherein the AR is unsubstituted, $-(CR^{60}R^{61})_mAR$ wherein the AR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AR is a cyclic or polycyclic aromatic or saturated or unsaturated non-aromatic ring containing from 3 to 16 carbon atoms and optionally containing from one to three heteroatoms, provided that when the ring is aromatic and the number of carbon atoms is 3 the ring contains at least two heteroatoms and when the ring is aromatic and the number of carbon atoms is 4 the ring contains at least one heteroatom, and R^{60} and R^{61} are independently selected from: hydrogen and C_{1-4}alkyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are C_{1-4}alkyl,

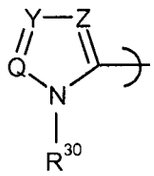
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, C_{1-4}alkyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and C_{1-4}alkyl; and

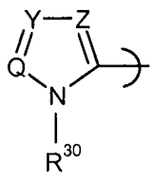
n is 0 to 2 and this moiety is optionally, if applicable, substituted by hydroxyC_{1-4}alkyl;



provided that one and only one of R^{41} and R^{42} is ;

and/or pharmaceutically acceptable salts thereof.

Included among the presently invented compounds of Formula (I) are those in which:

R^{41} and R^{42} are independently selected from: hydrogen,  , halogen, C_{1-4}alkyl, trifluoromethyl, methoxy, furan and thiophene,

where Q is nitrogen, Y is selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and $-C(R^{48})-$, provided that at most one of Y and Z are nitrogen, and

R^{30} is C_{1-4}alkyl,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, trifluoromethyl, aryl, heteroaryl, cylcoalkyl, heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl and methoxy;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAAR$ wherein the AAR is unsubstituted, $-(CR^{60}R^{61})_mAAR$ wherein the AAR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AAR is selected from phenyl, indole, naphthalene, pyridine and cyclohexyl, and

R^{60} and R^{61} are independently selected from: hydrogen and methyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are methyl,

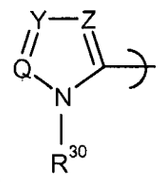
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, methyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and methyl; and

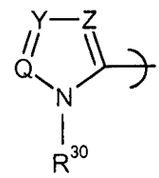
n is 1 to 2 and this moiety is optionally substituted by hydroxylmethyl;

provided that one and only one of R^{41} and R^{42} is 

;

and/or pharmaceutically acceptable salts thereof.

Included among the presently invented compounds of Formula (I) are those in which:



R^{41} and R^{42} are independently selected from: hydrogen, halogen, C_{1-4}alkyl, trifluoromethyl, methoxy and furan,

where Q is nitrogen, Y is selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and $-C(R^{48})-$, provided that at most one of Y and Z are nitrogen, and

R^{30} is C_{1-4}alkyl,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, trifluoromethyl, phenyl, cylcopropyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl and methoxy;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAAR$ wherein the AAR is unsubstituted, $-(CR^{60}R^{61})_mAAR$ wherein the AAR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AAR is selected from phenyl, indole, naphthalene, pyridine and cyclohexyl, and

R^{60} and R^{61} are independently selected from: hydrogen and methyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are methyl,

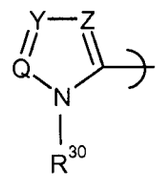
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, methyl and hydroxy;

X is selected from O, S and NR^{49},

where R^{49} is selected from hydrogen and methyl; and

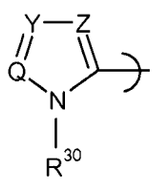
n is 1 to 2 and this moiety is optionally substituted by hydroxylmethyl;

provided that one and only one of R^{41} and R^{42} is  ;

and/or pharmaceutically acceptable salts thereof.

Included among the presently invented compounds of Formula (I) are those in which:

R^{41} is selected from: chlorine, ethyl, methyl and methoxy;

R^{42} is  ,

where Q is nitrogen, Y is –CH- and Z is $-C(R^{48})-$, and

R^{30} is selected from methyl and ethyl,

where R^{48} is selected from: hydrogen, methyl, chlorine and bromine;

R^{43} is hydrogen;

R^{44} is $-CH_2$-phenyl wherein the phenyl is substituted by one or two substituents selected from fluorine and trifluoromethyl;

R^{45} is hydrogen;

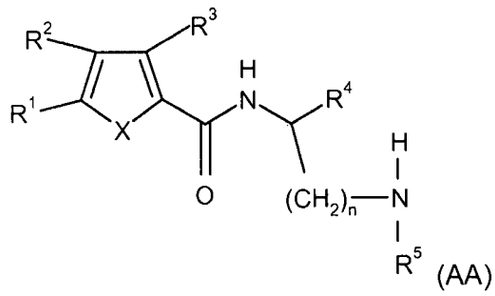
R^{20} is hydrogen;

X is selected from O and S; and

n is 1;

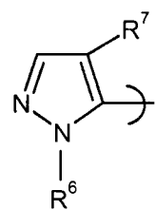
and/or pharmaceutically acceptable salts thereof.

Included in the presently invented compounds of Formula (I) are compounds of Formula (AA):



(AA)

wherein:

R^1 and R^2 are independently selected from: hydrogen,  ,

halogen, C_{1-4}alkyl, furan and thiophene,

where R^6 is C_{1-4}alkyl and R^7 is selected from hydrogen, C_{1-4}alkyl and halogen;

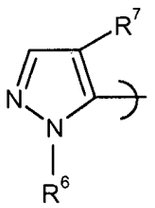
R^3 is selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

R^4 is selected from $-(CH_2)_m$aryl and $-(CH_2)_m$aryl wherein the aryl is substituted,
where m is 0 to 2;

R^5 is selected from hydrogen and C_{1-4}alkyl;

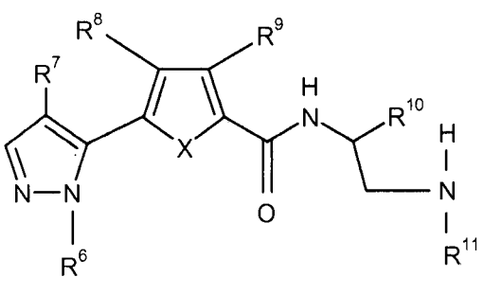
X is selected from O and S; and

n is 0 to 2;

provided that one and only one of R^1 and R^2 is  and further provided that at least one of R^1, R^2 and R^3 is hydrogen;

and/or pharmaceutically acceptable salts thereof.

Included in the presently invented compounds of Formula (I) are compounds of Formula (BB):



(BB)

wherein:

R^8 and R^9 are independently selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

R^6 is C_{1-4}alkyl;

R^7 is selected from hydrogen, C_{1-4}alkyl and halogen;

R^{10} is selected from: $-(CH_2)_mC_5$-C_{12}aryl and $-(CH_2)_mC_5$-C_{12}aryl wherein the aryl is substituted,
where m is 0 to 2;

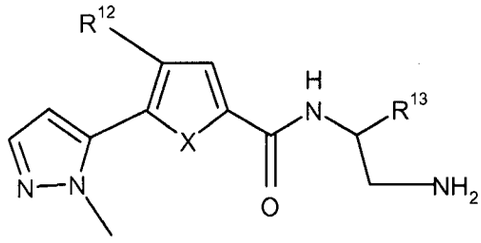
R^{11} is selected from hydrogen and C_{1-4}alkyl;

X is selected from O and S; and

provided that at least one of R^8 and R^9 is hydrogen;

and/or pharmaceutically acceptable salts thereof.

Included in the presently invented compounds of Formula (I) are compounds of Formula (CC):



(CC)

wherein:

R^{12} is selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

R^{13} is selected from: $-(CH_2)_m$phenyl and $-(CH_2)_m$phenyl wherein the phenyl is substituted,

where m is 0 to 2;

X is selected from O and S; and

and/or pharmaceutically acceptable salts thereof.

Included among the compounds useful in the present invention are:

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide;

N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(3-furanyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-N-[2-(methylamino)-1-phenylethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[1-(aminomethyl)-3-phenylpropyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-3-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-*N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-*N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

N-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-(methylamino)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(1*H*-indol-3-ylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(1-naphthalenyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(1-naphthalenyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(3-amino-1-phenylpropyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(3-pyridinylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*R*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-aminoethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-methylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[3-(trifluoromethyl)phenyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-[(1*S*)-1-(aminomethyl)-3-methylbutyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

(*N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-1,2,3-triazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*,2*S*)-2-amino-3-hydroxy-1-phenylpropyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide; and

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

and/or pharmaceutically acceptable salts thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

Certain of the compounds described herein may contain one or more chiral atoms, or may otherwise be capable of existing as two enantiomers. Accordingly, the compounds of this invention include mixtures of enantiomers as well as purified enantiomers or enantiomerically enriched mixtures. Also, it is understood that all tautomers and mixtures of tautomers are included within the scope of the compounds of Formula (I).

Certain compounds described herein may form a solvate which is understood to be a complex of variable stoichiometry formed by a solute (in this invention, a compound of Formula I a salt thereof) and a solvent. Such solvents for

the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include, without limitation, water, ethanol and acetic acid. Most preferably the solvent used is water.

By the term "aryl", and derivatives thereof, used alone or as part of a larger moiety as in "$-(CH_2)_m$aryl" as used herein, unless otherwise defined, is meant monocyclic, bicyclic, and tricyclic ring systems having a total of five to fourteen ring members, wherein at least one ring system is aromatic and wherein each ring in the system contains 3 to 7 members, such as phenyl, naphthalene, tetrahydronaphthalene and biphenyl.

Suitably, by the term "aryl" is meant a monocyclic aromatic ring system having a total of five to 7 ring members.

By the term "heteroaryl", and derivatives thereof, used alone or as part of a larger moiety as in "$-(CH_2)_m$heteroaryl" as used herein, unless otherwise defined, is meant a cyclic aromatic ring containing from 3 to 7 carbon atoms and containing from one to 3 heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms. Exemplary "heteroaryl" groups include pyridine and indole.

By the term " cycloalkyl", and derivatives thereof, used alone or as part of a larger moiety as in "$-(CH_2)_m$cycloalkyl" as used herein, unless otherwise defined, is meant a non-aromatic cyclic hydrocarbon ring having from three to seven carbon atoms. Exemplary "cycloalkyl" groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

By the term "heterocycloalkyl", and derivatives thereof, used alone or as part of a larger moiety as in "$-(CH_2)_m$heterocycloalkyl" as used herein, unless otherwise defined, is meant a non-aromatic cyclic hydrocarbon ring having from three to six carbon atoms and containing 1 or 2 heteroatoms. Exemplary "cycloalkyl" groups include piperazine and pyrrolidine.

By the term "C_5-C_{12}aryl", used alone or as part of a larger moiety as in "$-(CH_2)_mC_5$-C_{12}aryl", as used herein, is meant an aromatic group selected from: phenyl, naphthalene, tehrahydronaphthanlene and biphenyl.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has from one to five substituents, suitably from one to three substituents, selected from the group consisting of: $-CO_2R^{20}$, C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkyloxy, amino, C_1-C_4alkylamino, aminoC_1-C_4alkyl,

diC_1-C_4alkylamino, hydroxy, nitro, tetrazole, cyano, oxo, halogen and trifluoromethyl, where R^{20} is selected form hydrogen, C_1-C_4alkyl, and trifluoromethyl.

Suitably, the term "substituted" as used herein is meant that the subject chemical moiety has from one to three substituents, selected from the group consisting of: C_1-C_4alkyl, hydroxyC_1-C_4alkyl, C_1-C_4alkyloxy, amino, C_1-C_4alkylamino, aminoC_1-C_4alkyl, hydroxy, tetrazole, halogen and trifluoromethyl.

Suitably, the term "substituted" as used herein is meant that the subject chemical moiety has from one to three substituents, selected from the group consisting of: halogen and trifluoromethyl.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein, including alkyl chains defined by the term "-$(CH_2)_n$", "-$(CH_2)_m$" and the like, is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl as used herein include: -CH_3, -CH_2-CH_3, -CH_2-CH_2-CH_3, -$CH(CH_3)_2$, -CH_2-CH_2-$C(CH_3)_3$, -C≡C-$C(CH_3)_3$, -$C(CH_3)_3$, -$(CH_2)_3$-CH_3, -CH_2-$CH(CH_3)_2$, -$CH(CH_3)$-CH_2-CH_3, -CH=CH_2, and -C≡C-CH_3.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic and therapeutic therapy. Prophylactic therapy is appropriate, for example, when a subject is considered at high risk for developing cancer, or when a subject has been exposed to a carcinogen.

As used herein, the term "effective amount" and derivatives thereof means that amount of a drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal or human that is being sought, for instance, by a researcher or clinician. Furthermore, the term "therapeutically effective amount" and derivatives thereof means any amount which, as compared to a corresponding subject who has not received such amount, results in improved treatment, healing, prevention, or amelioration of a disease, disorder, or side effect, or a decrease in the rate of advancement of a disease or disorder. The term also includes within its scope amounts effective to enhance normal physiological function.

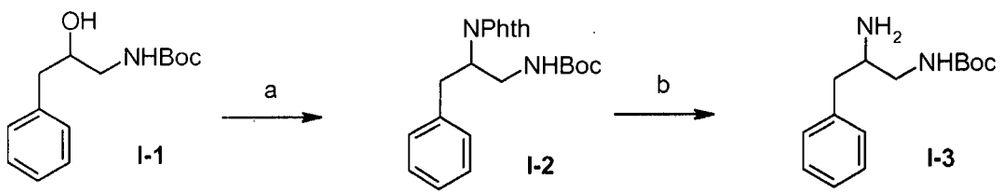
Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

The pharmaceutically acceptable salts of the compounds of the invention are readily prepared by those of skill in the art.

The novel compounds of Formulas (I), (AA), (BB) and (CC) are generally prepared as shown in Schemes 1 to 3 below, or by analogous methods, provided the X and 'R' substituents in Formulas (I), (AA), (BB) and (CC) respectively do not include any such substituents that render inoperative the processes of any of Schemes 1 to 3. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

General Schemes

Scheme 1



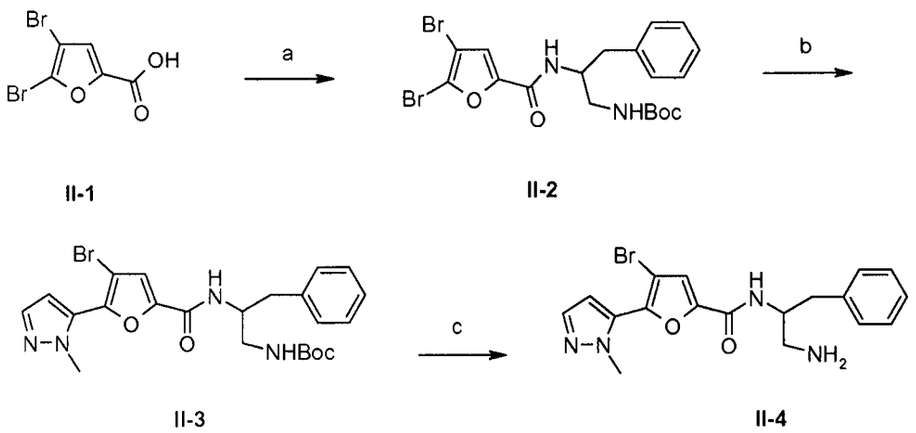
I-1 I-2 I-3

Reagents: (a) Phthalimide, PPh_3, DEAD, THF, RT; (b) NH_2NH_2, MeOH, 50 °C.

Amino alcohol (**I-1**) was reacted under Mitsunobu conditions to provide the differentially protected diamine (**I-2**). Mitsunobu reactions are well know to those skilled in the art of organic synthesis. Methods and reaction conditions for such transformations are discussed in *Synthesis* **1981**, 1-28. Selective deprotection of the phthalimide group of (**I-2**) using a nucleophilic amine such as hydrazine or methyl amine in a polar solvent such as methanol, afforded amine (**I-3**). Many different protecting groups are available to one skilled in the art and can be used here as long as they do not interfere with the processes listed herein. Methods for

the protection of amines are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience).

Scheme 2

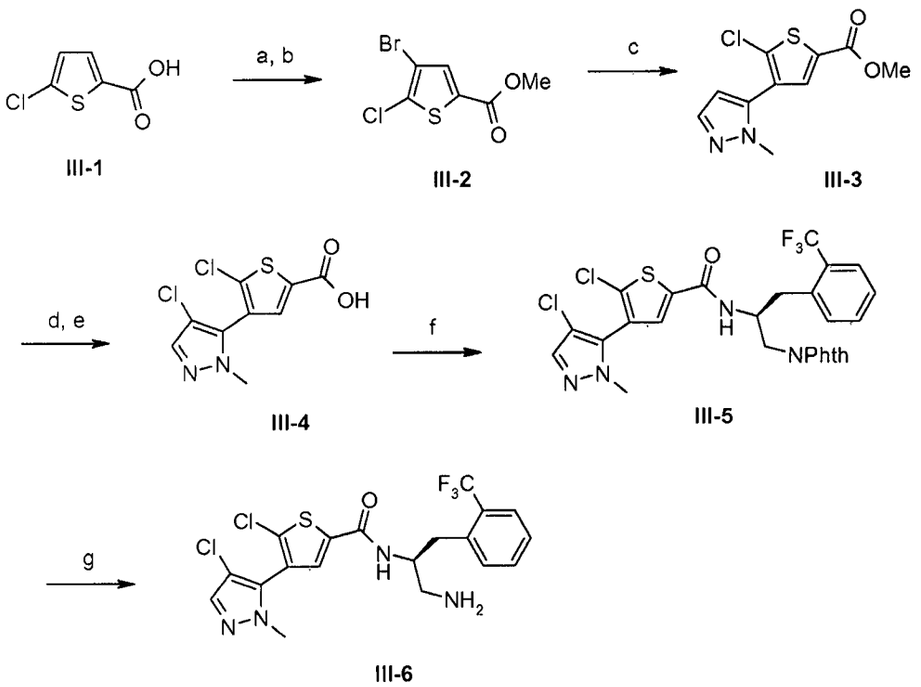


Reagents: (a) PyBrop, $(i\text{-}Pr)_2NEt$, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate, DCM, RT; (b) 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole, K_2CO_3, $Pd(PPh_3)_4$, dioxane/H_2O; (c) TFA / DCM, RT.

Carboxylic acid (**II-1**) was reacted with 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate to form amide (**II-2**). A variety of amide coupling reagents such as EDC, PyBrop, etc. are commercially available. Amide coupling reactions are generally run in solvents such as DCM or DMF, utilizing an organic base like Et_3N or $(i\text{-}Pr)_2NEt$. Dibromide (**II-2**) was regioselectively coupled with 1,1-dimethylethyl (2-{[(4,5-dibromo-2-furanyl)carbonyl]amino}-3-phenylpropyl)carbamate using a Suzuki coupling procedure. Suzuki-like couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an inorganic base, for example K_2CO_3, Na_2CO_3 or K_3PO_4, in an aqueous mixture containing ethereal solvents such as DME, dioxane, or THF. Methods for palladium-mediated couplings are described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by Wiley and sons). Acidic treatment of **II-3** with HCl or TFA to remove the Boc protecting group produced amine (**II-4**). Many different protecting groups are available to one skilled in the art and can be used here as long as they do not interfere with the processes listed herein. Methods

for the protection of amines are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience).

Scheme 3



Reagents: (a) MeOH, H_2SO_4, 60°C; (b) $AlCl_3$, Br_2, $CHCl_3$; (c) 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole, K_2CO_3, $Pd_2(t\text{-}Bu)_3$, dioxane/H_2O, 70°C; (d) NCS, THF, 70°C; (e) 6M NaOH, THF/MeOH, 50°C; (f) PyBrop, $(i\text{-}Pr)_2NEt$, 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione, DCM, RT; (g) NH_2NH_2, THF/MeOH, RT.

Carboxylic acid (**III-1**) was esterified under standard Fisher esterification conditions and then selectively halogenated with the aid of a Lewis acid to give (**III-2**). The dihalogenated ester was selectively coupled with 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole using Suzuki coupling chemistry to give (**III-3**). Suzuki-like couplings are typically run using a palladium(0) catalyst such as $Pd(PPh_3)_4$ with an inorganic base, for example K_2CO_3, Na_2CO_3 or K_3PO_4, in an aqueous mixture containing ethereal solvents such as DME, dioxane, or THF.

Methods for palladium-mediated couplings are described in standard reference volumes, such as Schlosser "Organometallics in Synthesis" (published by Wiley and sons). Ester (**III-3**) was chlorinated using NCS and *in situ* saponified using aqueous NaOH. The resulting carboxylic acid (**III-4**) was coupled with 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione to form amide (**III-5**). A variety of amide coupling reagents such as EDC, PyBrop, etc. are commercially available. Amide coupling reactions are generally run in solvents such as DCM or DMF, utilizing an organic base like Et_3N or $(i\text{-}Pr)_2NEt$. Amide (**III-5**) was deprotected using hydrazine to give amine (**III-6**). Many different protecting groups are available to one skilled in the art and can be used here as long as they do not interfere with the processes listed herein. Methods for the protection of amines are described in standard reference volumes, such as Greene "Protective Groups in Organic Synthesis" (published by Wiley-Interscience).

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Typically, any anti-neoplastic agent that has activity versus a susceptible tumor being treated may be co-administered in the treatment of cancer in the present invention. Examples of such agents can be found in Cancer Principles and Practice of Oncology by V.T. Devita and S. Hellman (editors), 6th edition (February 15, 2001), Lippincott Williams & Wilkins Publishers. A person of ordinary skill in the art would be able to discern which combinations of agents would be useful based on the particular characteristics of the drugs and the cancer involved. Typical anti-neoplastic agents useful in the present invention include, but are not limited to, anti-microtubule agents such as diterpenoids and vinca alkaloids; platinum coordination complexes; alkylating agents such as nitrogen mustards, oxazaphosphorines,

alkylsulfonates, nitrosoureas, and triazenes; antibiotic agents such as anthracyclins, actinomycins and bleomycins; topoisomerase II inhibitors such as epipodophyllotoxins; antimetabolites such as purine and pyrimidine analogues and anti-folate compounds; topoisomerase I inhibitors such as camptothecins; hormones and hormonal analogues; signal transduction pathway inhibitors; non-receptor tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

Examples of a further active ingredient or ingredients (anti-neoplastic agent) for use in combination or co-administered with the presently invented AKT inhibiting compounds are chemotherapeutic agents.

Anti-microtubule or anti-mitotic agents are phase specific agents active against the microtubules of tumor cells during M or the mitosis phase of the cell cycle. Examples of anti-microtubule agents include, but are not limited to, diterpenoids and vinca alkaloids.

Diterpenoids, which are derived from natural sources, are phase specific anti -cancer agents that operate at the G_2/M phases of the cell cycle. It is believed that the diterpenoids stabilize the β-tubulin subunit of the microtubules, by binding with this protein. Disassembly of the protein appears then to be inhibited with mitosis being arrested and cell death following. Examples of diterpenoids include, but are not limited to, paclitaxel and its analog docetaxel.

Paclitaxel, 5β,20-epoxy-1,2α,4,7β,10β,13α-hexa-hydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine; is a natural diterpene product isolated from the Pacific yew tree *Taxus brevifolia* and is commercially available as an injectable solution TAXOL®. It is a member of the taxane family of terpenes. It was first isolated in 1971 by Wani et al. J. Am. Chem, Soc., 93:2325. 1971), who characterized its structure by chemical and X-ray crystallographic methods. One mechanism for its activity relates to paclitaxel's capacity to bind tubulin, thereby inhibiting cancer cell growth. Schiff et al., Proc. Natl, Acad, Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol, Chem, 256: 10435-10441 (1981). For a review of synthesis and anticancer activity of some paclitaxel derivatives see: D. G. I. Kingston *et al.*, Studies in Organic Chemistry vol. 26, entitled "New trends in Natural Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) pp 219-235.

Paclitaxel has been approved for clinical use in the treatment of refractory ovarian cancer in the United States (Markman et al., Yale Journal of Biology and

Medicine, 64:583, 1991; McGuire et al., Ann. Intem, Med., 111:273,1989) and for the treatment of breast cancer (Holmes et al., J. Nat. Cancer Inst., 83:1797,1991.) It is a potential candidate for treatment of neoplasms in the skin (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) and head and neck carcinomas (Forastire et. al., Sem. Oncol., 20:56, 1990). The compound also shows potential for the treatment of polycystic kidney disease (Woo et. al., Nature, 368:750. 1994), lung cancer and malaria. Treatment of patients with paclitaxel results in bone marrow suppression (multiple cell lineages, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) related to the duration of dosing above a threshold concentration (50nM) (Kearns, C.M. et. al., Seminars in Oncology, 3(6) p.16-23, 1995).

Docetaxel, (2R,3S)- N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate; is commercially available as an injectable solution as TAXOTERE®. Docetaxel is indicated for the treatment of breast cancer. Docetaxel is a semisynthetic derivative of paclitaxel *q.v.*, prepared using a natural precursor, 10-deacetyl-baccatin III, extracted from the needle of the European Yew tree. The dose limiting toxicity of docetaxel is neutropenia.

Vinca alkaloids are phase specific anti-neoplastic agents derived from the periwinkle plant. Vinca alkaloids act at the M phase (mitosis) of the cell cycle by binding specifically to tubulin. Consequently, the bound tubulin molecule is unable to polymerize into microtubules. Mitosis is believed to be arrested in metaphase with cell death following. Examples of vinca alkaloids include, but are not limited to, vinblastine, vincristine, and vinorelbine.

Vinblastine, vincaleukoblastine sulfate, is commercially available as VELBAN® as an injectable solution. Although, it has possible indication as a second line therapy of various solid tumors, it is primarily indicated in the treatment of testicular cancer and various lymphomas including Hodgkin's Disease; and lymphocytic and histiocytic lymphomas. Myelosuppression is the dose limiting side effect of vinblastine.

Vincristine, vincaleukoblastine, 22-oxo-, sulfate, is commercially available as ONCOVIN® as an injectable solution. Vincristine is indicated for the treatment of acute leukemias and has also found use in treatment regimens for Hodgkin's and non-Hodgkin's malignant lymphomas. Alopecia and neurologic effects are the most common side effect of vincristine and to a lesser extent myelosupression and gastrointestinal mucositis effects occur.

Vinorelbine, 3',4'-didehydro -4'-deoxy-C'-norvincaleukoblastine [R-(R*,R*)-2,3-dihydroxybutanedioate (1:2)(salt)], commercially available as an injectable

solution of vinorelbine tartrate (NAVELBINE®), is a semisynthetic vinca alkaloid. Vinorelbine is indicated as a single agent or in combination with other chemotherapeutic agents, such as cisplatin, in the treatment of various solid tumors, particularly non-small cell lung, advanced breast, and hormone refractory prostate cancers. Myelosuppression is the most common dose limiting side effect of vinorelbine.

Platinum coordination complexes are non-phase specific anti-cancer agents, which are interactive with DNA. The platinum complexes enter tumor cells, undergo, aquation and form intra- and interstrand crosslinks with DNA causing adverse biological effects to the tumor. Examples of platinum coordination complexes include, but are not limited to, cisplatin and carboplatin.

Cisplatin, cis-diamminedichloroplatinum, is commercially available as PLATINOL® as an injectable solution. Cisplatin is primarily indicated in the treatment of metastatic testicular and ovarian cancer and advanced bladder cancer. The primary dose limiting side effects of cisplatin are nephrotoxicity, which may be controlled by hydration and diuresis, and ototoxicity.

Carboplatin, platinum, diammine [1,1-cyclobutane-dicarboxylate(2-)-O,O'], is commercially available as PARAPLATIN® as an injectable solution. Carboplatin is primarily indicated in the first and second line treatment of advanced ovarian carcinoma. Bone marrow suppression is the dose limiting toxicity of carboplatin.

Alkylating agents are non-phase anti-cancer specific agents and strong electrophiles. Typically, alkylating agents form covalent linkages, by alkylation, to DNA through nucleophilic moieties of the DNA molecule such as phosphate, amino, sulfhydryl, hydroxyl, carboxyl, and imidazole groups. Such alkylation disrupts nucleic acid function leading to cell death. Examples of alkylating agents include, but are not limited to, nitrogen mustards such as cyclophosphamide, melphalan, and chlorambucil; alkyl sulfonates such as busulfan; nitrosoureas such as carmustine; and triazenes such as dacarbazine.

Cyclophosphamide, 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, is commercially available as an injectable solution or tablets as CYTOXAN®. Cyclophosphamide is indicated as a single agent or in combination with other chemotherapeutic agents, in the treatment of malignant lymphomas, multiple myeloma, and leukemias. Alopecia, nausea, vomiting and leukopenia are the most common dose limiting side effects of cyclophosphamide.

Melphalan, 4-[bis(2-chloroethyl)amino]-L-phenylalanine, is commercially available as an injectable solution or tablets as ALKERAN®. Melphalan is

indicated for the palliative treatment of multiple myeloma and non-resectable epithelial carcinoma of the ovary. Bone marrow suppression is the most common dose limiting side effect of melphalan.

Chlorambucil, 4-[bis(2-chloroethyl)amino]benzenebutanoic acid, is commercially available as LEUKERAN® tablets. Chlorambucil is indicated for the palliative treatment of chronic lymphatic leukemia, and malignant lymphomas such as lymphosarcoma, giant follicular lymphoma, and Hodgkin's disease. Bone marrow suppression is the most common dose limiting side effect of chlorambucil.

Busulfan, 1,4-butanediol dimethanesulfonate, is commercially available as MYLERAN® TABLETS. Busulfan is indicated for the palliative treatment of chronic myelogenous leukemia. Bone marrow suppression is the most common dose limiting side effects of busulfan.

Carmustine, 1,3-[bis(2-chloroethyl)-1-nitrosourea, is commercially available as single vials of lyophilized material as BiCNU®. Carmustine is indicated for the palliative treatment as a single agent or in combination with other agents for brain tumors, multiple myeloma, Hodgkin's disease, and non-Hodgkin's lymphomas. Delayed myelosuppression is the most common dose limiting side effects of carmustine.

Dacarbazine, 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide, is commercially available as single vials of material as DTIC-Dome®. Dacarbazine is indicated for the treatment of metastatic malignant melanoma and in combination with other agents for the second line treatment of Hodgkin's Disease. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dacarbazine.

Antibiotic anti-neoplastics are non-phase specific agents, which bind or intercalate with DNA. Typically, such action results in stable DNA complexes or strand breakage, which disrupts ordinary function of the nucleic acids leading to cell death. Examples of antibiotic anti-neoplastic agents include, but are not limited to, actinomycins such as dactinomycin, anthrocyclins such as daunorubicin and doxorubicin; and bleomycins.

Dactinomycin, also know as Actinomycin D, is commercially available in injectable form as COSMEGEN®. Dactinomycin is indicated for the treatment of Wilm's tumor and rhabdomyosarcoma. Nausea, vomiting, and anorexia are the most common dose limiting side effects of dactinomycin.

Daunorubicin, (8S-cis-)-8-acetyl-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as a liposomal

injectable form as DAUNOXOME® or as an injectable as CERUBIDINE®. Daunorubicin is indicated for remission induction in the treatment of acute nonlymphocytic leukemia and advanced HIV associated Kaposi's sarcoma. Myelosuppression is the most common dose limiting side effect of daunorubicin.

Doxorubicin, (8S, 10S)-10-[(3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranosyl)oxy]-8-glycoloyl, 7,8,9,10-tetrahydro-6,8,11-trihydroxy-1-methoxy-5,12 naphthacenedione hydrochloride, is commercially available as an injectable form as RUBEX® or ADRIAMYCIN RDF®. Doxorubicin is primarily indicated for the treatment of acute lymphoblastic leukemia and acute myeloblastic leukemia, but is also a useful component in the treatment of some solid tumors and lymphomas. Myelosuppression is the most common dose limiting side effect of doxorubicin.

Bleomycin, a mixture of cytotoxic glycopeptide antibiotics isolated from a strain of *Streptomyces verticillus*, is commercially available as BLENOXANE®. Bleomycin is indicated as a palliative treatment, as a single agent or in combination with other agents, of squamous cell carcinoma, lymphomas, and testicular carcinomas. Pulmonary and cutaneous toxicities are the most common dose limiting side effects of bleomycin.

Topoisomerase II inhibitors include, but are not limited to, epipodophyllotoxins.

Epipodophyllotoxins are phase specific anti-neoplastic agents derived from the mandrake plant. Epipodophyllotoxins typically affect cells in the S and G_2 phases of the cell cycle by forming a ternary complex with topoisomerase II and DNA causing DNA strand breaks. The strand breaks accumulate and cell death follows. Examples of epipodophyllotoxins include, but are not limited to, etoposide and teniposide.

Etoposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-ethylidene-β-D-glucopyranoside], is commercially available as an injectable solution or capsules as VePESID® and is commonly known as VP-16. Etoposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of testicular and non-small cell lung cancers. Myelosuppression is the most common side effect of etoposide. The incidence of leucopenia tends to be more severe than thrombocytopenia.

Teniposide, 4'-demethyl-epipodophyllotoxin 9[4,6-0-(R)-thenylidene-β-D-glucopyranoside], is commercially available as an injectable solution as VUMON® and is commonly known as VM-26. Teniposide is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia in

children. Myelosuppression is the most common dose limiting side effect of teniposide. Teniposide can induce both leucopenia and thrombocytopenia.

Antimetabolite neoplastic agents are phase specific anti-neoplastic agents that act at S phase (DNA synthesis) of the cell cycle by inhibiting DNA synthesis or by inhibiting purine or pyrimidine base synthesis and thereby limiting DNA synthesis. Consequently, S phase does not proceed and cell death follows. Examples of antimetabolite anti-neoplastic agents include, but are not limited to, fluorouracil, methotrexate, cytarabine, mecaptopurine, thioguanine, and gemcitabine.

5-fluorouracil, 5-fluoro-2,4- (1H,3H) pyrimidinedione, is commercially available as fluorouracil. Administration of 5-fluorouracil leads to inhibition of thymidylate synthesis and is also incorporated into both RNA and DNA. The result typically is cell death. 5-fluorouracil is indicated as a single agent or in combination with other chemotherapy agents in the treatment of carcinomas of the breast, colon, rectum, stomach and pancreas. Myelosuppression and mucositis are dose limiting side effects of 5-fluorouracil. Other fluoropyrimidine analogs include 5-fluoro deoxyuridine (floxuridine) and 5-fluorodeoxyuridine monophosphate.

Cytarabine, 4-amino-1-β-D-arabinofuranosyl-2 (1H)-pyrimidinone, is commercially available as CYTOSAR-U® and is commonly known as Ara-C. It is believed that cytarabine exhibits cell phase specificity at S-phase by inhibiting DNA chain elongation by terminal incorporation of cytarabine into the growing DNA chain. Cytarabine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Other cytidine analogs include 5-azacytidine and 2',2'-difluorodeoxycytidine (gemcitabine). Cytarabine induces leucopenia, thrombocytopenia, and mucositis.

Mercaptopurine, 1,7-dihydro-6H-purine-6-thione monohydrate, is commercially available as PURINETHOL®. Mercaptopurine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Mercaptopurine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression and gastrointestinal mucositis are expected side effects of mercaptopurine at high doses. A useful mercaptopurine analog is azathioprine.

Thioguanine, 2-amino-1,7-dihydro-6H-purine-6-thione, is commercially available as TABLOID®. Thioguanine exhibits cell phase specificity at S-phase by inhibiting DNA synthesis by an as of yet unspecified mechanism. Thioguanine is indicated as a single agent or in combination with other chemotherapy agents in the treatment of acute leukemia. Myelosuppression, including leucopenia,

thrombocytopenia, and anemia, is the most common dose limiting side effect of thioguanine administration. However, gastrointestinal side effects occur and can be dose limiting. Other purine analogs include pentostatin, erythrohydroxynonyladenine, fludarabine phosphate, and cladribine.

Gemcitabine, 2'-deoxy-2', 2'-difluorocytidine monohydrochloride (β-isomer), is commercially available as GEMZAR®. Gemcitabine exhibits cell phase specificity at S-phase and by blocking progression of cells through the G1/S boundary. Gemcitabine is indicated in combination with cisplatin in the treatment of locally advanced non-small cell lung cancer and alone in the treatment of locally advanced pancreatic cancer. Myelosuppression, including leucopenia, thrombocytopenia, and anemia, is the most common dose limiting side effect of gemcitabine administration.

Methotrexate, N-[4[[(2,4-diamino-6-pteridinyl) methyl]methylamino] benzoyl]-L-glutamic acid, is commercially available as methotrexate sodium. Methotrexate exhibits cell phase effects specifically at S-phase by inhibiting DNA synthesis, repair and/or replication through the inhibition of dyhydrofolic acid reductase which is required for synthesis of purine nucleotides and thymidylate. Methotrexate is indicated as a single agent or in combination with other chemotherapy agents in the treatment of choriocarcinoma, meningeal leukemia, non-Hodgkin's lymphoma, and carcinomas of the breast, head, neck, ovary and bladder. Myelosuppression (leucopenia, thrombocytopenia, and anemia) and mucositis are expected side effect of methotrexate administration.

Camptothecins, including, camptothecin and camptothecin derivatives are available or under development as Topoisomerase I inhibitors. Camptothecins cytotoxic activity is believed to be related to its Topoisomerase I inhibitory activity. Examples of camptothecins include, but are not limited to irinotecan, topotecan, and the various optical forms of 7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20-camptothecin described below.

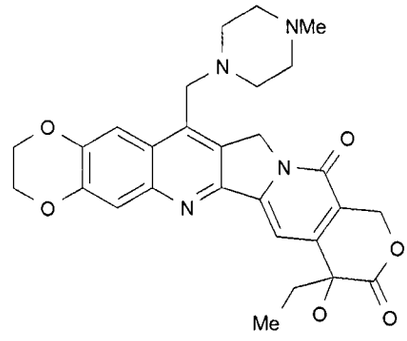
Irinotecan HCl, (4S)-4,11-diethyl-4-hydroxy-9-[(4-piperidinopiperidino) carbonyloxy]-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione hydrochloride, is commercially available as the injectable solution CAMPTOSAR®.

Irinotecan is a derivative of camptothecin which binds, along with its active metabolite SN-38, to the topoisomerase I – DNA complex. It is believed that cytotoxicity occurs as a result of irreparable double strand breaks caused by interaction of the topoisomerase I: DNA: irintecan or SN-38 ternary complex with replication enzymes. Irinotecan is indicated for treatment of metastatic cancer of

the colon or rectum. The dose limiting side effects of irinotecan HCl are myelosuppression, including neutropenia, and GI effects, including diarrhea.

Topotecan HCl, (S)-10-[(dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyrano[3',4',6,7]indolizino[1,2-b]quinoline-3,14-(4H,12H)-dione monohydrochloride, is commercially available as the injectable solution HYCAMTIN®. Topotecan is a derivative of camptothecin which binds to the topoisomerase I – DNA complex and prevents religation of singles strand breaks caused by Topoisomerase I in response to torsional strain of the DNA molecule. Topotecan is indicated for second line treatment of metastatic carcinoma of the ovary and small cell lung cancer. The dose limiting side effect of topotecan HCl is myelosuppression, primarily neutropenia.

Also of interest, is the camptothecin derivative of formula A following, currently under development, including the racemic mixture (R,S) form as well as the R and S enantiomers:



A

known by the chemical name "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R,S)-camptothecin (racemic mixture) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(R)-camptothecin (R enantiomer) or "7-(4-methylpiperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin (S enantiomer): Such compound as well as related compounds are described, including methods of making, in U.S. Patent Nos. 6,063,923; 5,342,947; 5,559,235; 5,491,237 and pending U.S. patent Application No. 08/977,217 filed November 24, 1997.

Hormones and hormonal analogues are useful compounds for treating cancers in which there is a relationship between the hormone(s) and growth and/or lack of growth of the cancer. Examples of hormones and hormonal analogues useful in cancer treatment include, but are not limited to, adrenocorticosteroids such as prednisone and prednisolone which are useful in the treatment of malignant lymphoma and acute leukemia in children; aminoglutethimide and other aromatase inhibitors such as anastrozole, letrazole, vorazole, and exemestane useful in the

treatment of adrenocortical carcinoma and hormone dependent breast carcinoma containing estrogen receptors; progestrins such as megestrol acetate useful in the treatment of hormone dependent breast cancer and endometrial carcinoma; estrogens, androgens, and anti-androgens such as flutamide, nilutamide, bicalutamide, cyproterone acetate and 5α-reductases such as finasteride and dutasteride, useful in the treatment of prostatic carcinoma and benign prostatic hypertrophy; anti-estrogens such as tamoxifen, toremifene, raloxifene, droloxifene, iodoxyfene, as well as selective estrogen receptor modulators (SERMS) such those described in U.S. Patent Nos. 5,681,835, 5,877,219, and 6,207,716, useful in the treatment of hormone dependent breast carcinoma and other susceptible cancers; and gonadotropin-releasing hormone (GnRH) and analogues thereof which stimulate the release of leutinizing hormone (LH) and/or follicle stimulating hormone (FSH) for the treatment prostatic carcinoma, for instance, LHRH agonists and antagagonists such as goserelin acetate and luprolide.

Signal transduction pathway inhibitors are those inhibitors, which block or inhibit a chemical process which evokes an intracellular change. As used herein this change is cell proliferation or differentiation. Signal tranduction inhibitors useful in the present invention include inhibitors of receptor tyrosine kinases, non-receptor tyrosine kinases, SH2/SH3domain blockers, serine/threonine kinases, phosphotidyl inositol-3 kinases, myo-inositol signaling, and Ras oncogenes.

Several protein tyrosine kinases catalyse the phosphorylation of specific tyrosyl residues in various proteins involved in the regulation of cell growth. Such protein tyrosine kinases can be broadly classified as receptor or non-receptor kinases.

Receptor tyrosine kinases are transmembrane proteins having an extracellular ligand binding domain, a transmembrane domain, and a tyrosine kinase domain. Receptor tyrosine kinases are involved in the regulation of cell growth and are generally termed growth factor receptors. Inappropriate or uncontrolled activation of many of these kinases, i.e. aberrant kinase growth factor receptor activity, for example by over-expression or mutation, has been shown to result in uncontrolled cell growth. Accordingly, the aberrant activity of such kinases has been linked to malignant tissue growth. Consequently, inhibitors of such kinases could provide cancer treatment methods. Growth factor receptors include, for example, epidermal growth factor receptor (EGFr), platelet derived growth factor receptor (PDGFr), erbB2, erbB4, vascular endothelial growth factor receptor (VEGFr), tyrosine kinase with immunoglobulin-like and epidermal growth factor homology domains (TIE-2), insulin growth factor –I (IGFI) receptor, macrophage

colony stimulating factor (cfms), BTK, ckit, cmet, fibroblast growth factor (FGF) receptors, Trk receptors (TrkA, TrkB, and TrkC), ephrin (eph) receptors, and the RET protooncogene. Several inhibitors of growth receptors are under development and include ligand antagonists, antibodies, tyrosine kinase inhibitors and anti-sense oligonucleotides. Growth factor receptors and agents that inhibit growth factor receptor function are described, for instance, in Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 February 1997; and Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul and Kerr, David, CRC press 1994, London.

Tyrosine kinases, which are not growth factor receptor kinases are termed non-receptor tyrosine kinases. Non-receptor tyrosine kinases for use in the present invention, which are targets or potential targets of anti-cancer drugs, include cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (Focal adhesion kinase), Brutons tyrosine kinase, and Bcr-Abl. Such non-receptor kinases and agents which inhibit non-receptor tyrosine kinase function are described in Sinh, S. and Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; and Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

SH2/SH3 domain blockers are agents that disrupt SH2 or SH3 domain binding in a variety of enzymes or adaptor proteins including, PI3-K p85 subunit, Src family kinases, adaptor molecules (Shc, Crk, Nck, Grb2) and Ras-GAP. SH2/SH3 domains as targets for anti-cancer drugs are discussed in Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

Inhibitors of Serine/Threonine Kinases including MAP kinase cascade blockers which include blockers of Raf kinases (rafk), Mitogen or Extracellular Regulated Kinase (MEKs), and Extracellular Regulated Kinases (ERKs); and Protein kinase C family member blockers including blockers of PKCs (alpha, beta, gamma, epsilon, mu, lambda, iota, zeta). IkB kinase family (IKKa, IKKb), PKB family kinases, akt kinase family members, and TGF beta receptor kinases. Such Serine/Threonine kinases and inhibitors thereof are described in Yamamoto, T., Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., and Navab, R. (2000), Biochemical Pharmacology, 60. 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., and Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; U.S. Patent No. 6,268,391; and Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

Inhibitors of Phosphotidyl inositol-3 Kinase family members including blockers of PI3-kinase, ATM, DNA-PK, and Ku may also be useful in the present invention. Such kinases are discussed in Abraham, R.T. (1996), Current Opinion in Immunology. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), Oncogene 17 (25) 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; and Zhong, H. et al, Cancer res, (2000) 60(6), 1541-1545.

Also of interest in the present invention are Myo-inositol signaling inhibitors such as phospholipase C blockers and Myoinositol analogues. Such signal inhibitors are described in Powis, G., and Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman and David Kerr, CRC press 1994, London.

Another group of signal transduction pathway inhibitors are inhibitors of Ras Oncogene. Such inhibitors include inhibitors of farnesyltransferase, geranyl-geranyl transferase, and CAAX proteases as well as anti-sense oligonucleotides, ribozymes and immunotherapy. Such inhibitors have been shown to block ras activation in cells containing wild type mutant ras, thereby acting as antiproliferation agents. Ras oncogene inhibition is discussed in Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 – 102; and BioChim. Biophys. Acta, (19899) 1423(3):19-30.

As mentioned above, antibody antagonists to receptor kinase ligand binding may also serve as signal transduction inhibitors. This group of signal transduction pathway inhibitors includes the use of humanized antibodies to the extracellular ligand binding domain of receptor tyrosine kinases. For example Imclone C225 EGFR specific antibody (see Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); Herceptin ® erbB2 antibody (see Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases, Breast Cancer Res., 2000, 2(3), 176-183); and 2CB VEGFR2 specific antibody (see Brekken, R.A. et al. Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

Non-receptor kinase angiogenesis inhibitors may also be useful in the present invention. Inhibitors of angiogenesis related VEGFR and TIE2 are discussed above in regard to signal transduction inhibitors (both receptors are receptor tyrosine kinases). Angiogenesis in general is linked to erbB2/EGFR signaling since inhibitors of erbB2 and EGFR have been shown to inhibit angiogenesis, primarily VEGF expression. Accordingly, non-receptor tyrosine

kinase inhibitors may be used in combination with the compounds of the present invention. For example, anti-VEGF antibodies, which do not recognize VEGFR (the receptor tyrosine kinase), but bind to the ligand; small molecule inhibitors of integrin ($alpha_v$ $beta_3$) that will inhibit angiogenesis; endostatin and angiostatin (non-RTK) may also prove useful in combination with the disclosed compounds. (See Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, and Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

Agents used in immunotherapeutic regimens may also be useful in combination with the compounds of formula (I). There are a number of immunologic strategies to generate an immune response. These strategies are generally in the realm of tumor vaccinations. The efficacy of immunologic approaches may be greatly enhanced through combined inhibition of signaling pathways using a small molecule inhibitor. Discussion of the immunologic/tumor vaccine approach against erbB2/EGFR are found in Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; and Chen Y, Hu D, Eling DJ, Robbins J, and Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

Agents used in proapoptotic regimens (e.g., bcl-2 antisense oligonucleotides) may also be used in the combination of the present invention. Members of the Bcl-2 family of proteins block apoptosis. Upregulation of bcl-2 has therefore been linked to chemoresistance. Studies have shown that the epidermal growth factor (EGF) stimulates anti-apoptotic members of the bcl-2 family (i.e., mcl-1). Therefore, strategies designed to downregulate the expression of bcl-2 in tumors have demonstrated clinical benefit and are now in Phase II/III trials, namely Genta's G3139 bcl-2 antisense oligonucleotide. Such proapoptotic strategies using the antisense oligonucleotide strategy for bcl-2 are discussed in Water JS et al. (2000), J. Clin. Oncol. 18: 1812-1823; and Kitada S et al. (1994), Antisense Res. Dev. 4: 71-79.

Cell cycle signalling inhibitors inhibit molecules involved in the control of the cell cycle. A family of protein kinases called cyclin dependent kinases (CDKs) and their interaction with a family of proteins termed cyclins controls progression through the eukaryotic cell cycle. The coordinate activation and inactivation of different cyclin/CDK complexes is necessary for normal progression through the cell cycle. Several inhibitors of cell cycle signalling are under development. For instance, examples of cyclin dependent kinases, including CDK2, CDK4, and CDK6 and inhibitors for the same are described in, for instance, Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

In one embodiment, the cancer treatment method of the claimed invention includes the co-administration a compound of Formula (I) and/or a pharmaceutically acceptable salt thereof and at least one anti-neoplastic agent, such as one selected from the group consisting of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors, non-receptor tyrosine kinase angiogenesis inhibitors, immunotherapeutic agents, proapoptotic agents, and cell cycle signaling inhibitors.

Because the pharmaceutically active compounds of the present invention are active as AKT inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid,

Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

Suitably, the present invention relates to a method for treating or lessening the severity of a cancer selected from ovarian, breast, pancreatic and prostate.

Isolation and Purification of His-tagged AKT1 (aa 136-480)

Insect cells expressing His-tagged AKT1 (aa 136-480) were lysed in 25 mM HEPES, 100 mM NaCl, 20 mM imidazole; pH 7.5 using a polytron (5 mLs lysis buffer/g cells). Cell debris was removed by centrifuging at 28,000 x *g* for 30 minutes. The supernatant was filtered through a 4.5-micron filter then loaded onto a nickel-chelating column pre-equilibrated with lysis buffer. The column was washed with 5 column volumes (CV) of lysis buffer then with 5 CV of 20% buffer B, where buffer B is 25 mM HEPES, 100 mM NaCl, 300 mM imidazole; pH 7.5. His-tagged AKT1 (aa 136-480) was eluted with a 20-100% linear gradient of buffer B over 10 CV. His-tagged AKT1 (136-480) eluting fractions were pooled and diluted 3-fold with buffer C, where buffer C is 25 mM HEPES, pH 7.5. The sample was then chromatographed over a Q-Sepharose HP column pre-equilibrated with buffer C. The column was washed with 5 CV of buffer C then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl; pH 7.5. His-tagged AKT1 (aa 136-480) containing fractions were pooled and concentrated in a 10-kDa molecular weight cutoff concentrator. His-tagged AKT1 (aa 136-480) was chromatographed over a Superdex 75 gel filtration column pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 1 mM DTT; pH 7.5. His-tagged AKT1 (aa 136-480) fractions were examined using SDS-PAGE and mass spec. The protein was pooled, concentrated and frozen at –80C.

His-tagged AKT2 (aa 138-481) and His-tagged AKT3 (aa 135-479) were isolated and purified in a similar fashion.

His-tagged AKT Enzyme Assay

Compounds of the present invention were tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine

residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation was detected by the following procedure:

Assays were performed in 384well U-bottom white plates. 10 nM activated AKT enzyme was incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction was stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate was sealed, the beads were allowed to settle overnight, and then the plate was counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses were plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: y = ((Vmax * x) / (K + x)) where Vmax is the upper asymptote and K is the IC50.

Cloning of full-length human (FL) AKT1:

Full-length human AKT1 gene was amplified by PCR from a plasmid containing myristylated-AKT1-ER (gift from Robert T. Abraham, Duke University under MTA, described in Klippel et al. in Molecular and Cellular Biology 1998 Volume 18 p.5699) using the 5' primer: SEQ.ID NO: 2, 5' TATATAGGATCCATGAGCGACGTGGC 3' and the 3' primer: SEQ.ID NO: 3, AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. The 5' primer included a BamHI site and the 3'primer included an XhoI site for cloning purposes. The resultant PCR product was subcloned in pcDNA3 as a BamHI / XhoI fragment. A mutation in the sequence (TGC) coding for a Cysteine^{25} was converted to the wild-type AKT1 sequence (CGC) coding for an Arginine^{25} by site-directed mutagenesis using the QuikChange® Site Directed Mutagenesis Kit (Stratagene). The AKT1 mutagenic primer: SEQ.ID NO: 4, 5' ACCTGGCGGCCACGCTACTTCCTCC and selection primer: SEQ.ID NO: 5, 5' CTCGAGCATGCAACTAGAGGGCC (designed to destroy

an XbaI site in the multiple cloning site of pcDNA3) were used according to manufacturer's suggestions. For expression/purification purposes, AKT1 was isolated as a BamHI / XhoI fragment and cloned into the BamHI / XhoI sites of pFastbacHTb (Invitrogen).

Expression of FL human AKT1:

Expression was done using the BAC-to-BAC Baculovirus Expression System from Invitrogen (catalog # 10359-016). Briefly 1) the cDNA was transferred from the FastBac vector into bacmid DNA, 2) the bacmid DNA was isolated and used to transfect Sf9 insect cells, 3) the virus was produced in Sf9 cells, 4) T. ni cells were infected with this virus and sent for purification.

Purification of FL human AKT1:

For the purification of full-length AKT1, 130 g sf9 cells (batch # 41646W02) were resuspended in lysis buffer (buffer A, 1L, pH 7.5) containing 25 mM HEPES, 100 mM NaCl, and 20 mM imidazole. The cell lysis was carried out by Avestin (2 passes at 15K-20K psi). Cell debris was removed by centrifuging at 16K rpm for 1 hour and the supernatant was batch bound to 10 ml Nickel Sepharose HP beads at 4 C for over night. The beads were then transferred to column and the bound material was eluted with buffer B (25 mM HEPES, 100 mM NaCl, 300 mM imidazole, pH 7.5). AKT eluting fractions were pooled and diluted 3 fold using buffer C (25 mM HEPES, 5 mM DTT; pH 7.5). The sample was filtered and chromatographed over a 10 mL Q-HP column pre-equilibrated with buffer C at 2 mL/min.

The Q-HP column was washed with 3 column volume (CV) of buffer C, then step eluted with 5 CV 10%D, 5 CV 20% D, 5 CV 30% D, 5 CV 50% D and 5 CV of 100% D; where buffer D is 25 mM HEPES, 1000 mM NaCl, 5 mM DTT; pH 7.5. 5 mL fractions collected. AKT containing fractions were pooled and concentrated to 5 ml. The protein was next loaded to a 120 ml Superdex 75 sizing column that was pre-equilibrated with 25 mM HEPES, 200 mM NaCl, 5 mM DTT; pH 7.5. 2.5 mL fractions were collected.

AKT 1 eluting fractions were pooled, aliquoted (1 ml) and stored at –80C. Mass spec and SDS-PAGE analysis were used to confirm purity and identity of the purified full-length AKT1.

Full length AKT2 and full length AKT3 were cloned, expressed and purified in a similar fashion.

AKT Enzyme Assay

Compounds of the present invention are tested for AKT 1, 2, and 3 protein serine kinase inhibitory activity in substrate phosphorylation assays. This assay examines the ability of small molecule organic compounds to inhibit the serine phosphorylation of a peptide substrate. The substrate phosphorylation assays use the catalytic domains of AKT 1, 2, or 3. AKT 1, 2 and 3 are also commercially available from Upstate USA, Inc. The method measures the ability of the isolated enzyme to catalyze the transfer of the gamma-phosphate from ATP onto the serine residue of a biotinylated synthetic peptide SEQ. ID NO: 1 (Biotin-ahx-ARKRERAYSFGHHA-amide). Substrate phosphorylation is detected by the following procedure:

Assays are performed in 384well U-bottom white plates. 10 nM activated AKT enzyme is incubated for 40 minutes at room temperature in an assay volume of 20ul containing 50mM MOPS, pH 7.5, 20mM $MgCl_2$, 4uM ATP, 8uM peptide, 0.04 uCi [g-^{33}P] ATP/well, 1 mM CHAPS, 2 mM DTT, and 1ul of test compound in 100% DMSO. The reaction is stopped by the addition of 50 ul SPA bead mix (Dulbecco's PBS without Mg^{2+} and Ca^{2+}, 0.1% Triton X-100, 5mM EDTA, 50uM ATP, 2.5mg/ml Streptavidin-coated SPA beads.) The plate is sealed, the beads are allowed to settle overnight, and then the plate is counted in a Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

The data for dose responses are plotted as % Control calculated with the data reduction formula 100*(U1-C2)/(C1-C2) versus concentration of compound where U is the unknown value, C1 is the average control value obtained for DMSO, and C2 is the average control value obtained for 0.1M EDTA. Data are fitted to the curve described by: y = ((Vmax * x) / (K + x)) where Vmax is the upper asymptote and K is the IC50.

Compounds of the invention are tested for activity against AKT1, AKT2, and AKT3 in one or more of the above assays.

The majority of the compounds of the Examples were tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: ≥ 5.9 against full length AKT1; ≥ 5.0 against full length AKT2; and ≥ 5.0 against full length AKT3.

The compounds of Examples 31, 32, 91, 95, 120, 128, 140, 161, 167, 169, 170, 190, 222, 225, 237, 249, 258 and 259 were tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: ≥ 8.6 against full length AKT1; and ≥ 7.5 against full length AKT2. The majority of the compounds of Examples 31, 32, 91, 95, 120, 128, 140, 161, 167, 169, 170, 190, 222, 225, 237, 249, 258 and 259 were tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value; ≥ 7.6 against full length AKT3.

The compound of Example 96 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 9.0 against full length AKT1; equal to 8.0 against full length AKT2; and equal to 8.8 against full length AKT3.

The compound of Example 137 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 9.0 against full length AKT1; equal to 7.8 against full length AKT2; and equal to 8.4 against full length AKT3.

The compound of Example 224 was tested generally according to the above AKT enzyme assays and in at least one experimential run exhibited a pIC50 value: equal to 8.7 against full length AKT1; and equal to 7.8 against full length AKT2.

The compound of Example 161 was tested generally according to the above AKT enzyme assays and in at least one experimental run exhibited a pIC50 value: equal to 8.8 against full length AKT1; equal to 7.5 against full length AKT2; and equal to 7.6 against full length AKT3.

The compound of Example 222 was tested generally according to the above AKT enzyme assays and in at least one experimential run exhibited a pIC50 value: equal to 8.8 against full length AKT1; and equal to 7.9 against full length AKT2; and equal to 8.5 against full length AKT3.

In the above data, pIC50 is defined as -log(IC50) where the IC50 value is expressed in molar units.

The pharmaceutically active compounds within the scope of this invention are useful as AKT inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring AKT inhibition, which comprises administering an effective compound of Formula (I) and/or a pharmaceutically acceptable salt, hydrate, solvate or pro-drug thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages, is preferred.

Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

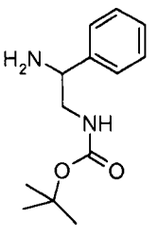
Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental Details

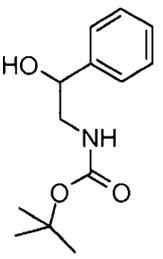
The compounds of Examples 1 to 328 are readily made according to Schemes 1 to 3 or by analogous methods.

Preparation 1

Preparation of 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate

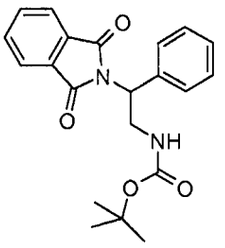


a) 1,1-dimethylethyl (2-hydroxy-2-phenylethyl)carbamate



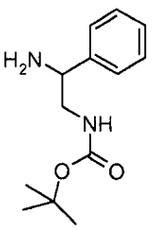
To a solution of 2-amino-1-phenylethanol (5 g, 36.4 mmol) in THF (182 mL) at 25 °C was added Boc_2O (8.7 g, 40.1 mmol) in one portion. After 0.5h, the solution was concentrated and the residue used directly without further purification: LC-MS (ES) m/z = 238 $(M+H)^+$.

b) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-phenylethyl]carbamate



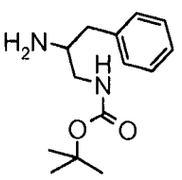
To a solution of 1,1-dimethylethyl (2-hydroxy-2-phenylethyl)carbamate (2 g, 8.44 mmol), phthalimide (1 g, 7.03 mmol) and triphenylphosphine (2.76 g, 10.5 mmol) in THF (35 mL) at 25 °C was added DEAD (1.7 mL, 10.5 mmol) dropwise. After 0.5h, the solution was concentrated and purified via column chromatography (silica, 15 % EtOAc in hexanes) affording the title compound (2 g, 80%) as a white foam: LC-MS (ES) m/z = 367 $(M+H)^+$.

c) 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate



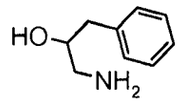
A solution of 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-phenylethyl]carbamate (2 g, 5.46 mmol) and either $MeNH_2$ (40wt% in H_2O, 10eq.) or NH_2NH_2 (10eq.) in MeOH (0.5M, 10 mL) was heated to 60 °C in a sealed tube. After 12h, the solution was concentrated and purified via column chromatography (silica-dry load, 2% MeOH in DCM (1% NH_4OH)) affording the title compound (1.1 g, 85%) as a white solid: LC-MS (ES) m/z = 237 $(M+H)^+$.

Preparation 2



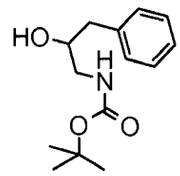
Preparation of 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate

a) 1-amino-3-phenyl-2-propanol



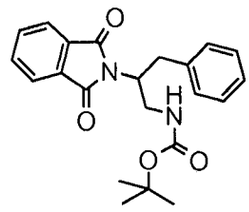
A solution of 2-(phenylmethyl)oxirane (7.5 g, 56.3 mmol) in NH_4OH (100 mL) was stirred at 25 °C in a sealed tube. After 12h, the solution was concentrated and used directly: LCMS (ES) m/e 152 $(M+H)^+$.

b) 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)carbamate



To a solution of 1-amino-3-phenyl-2-propanol (7.6 g, 50 mmole) in THF (50 mL) at RT was added $(Boc)_2O$ (12.0 g, 55 mmole). After stirring at RT for 2 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (5% MeOH in DCM (0.5% NH_4OH)) affording the title compound (13.1 g, 91%) as a clear yellow oil: LCMS (ES) m/z 252 $(M+H)^+$.

c) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]carbamate

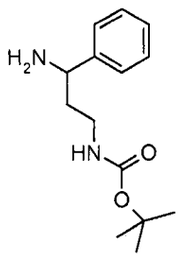


To a solution of 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)carbamate (10.0 g, 39.8 mmol), PPh_3 (12.5 g, 47.8 mmol) and phthalimide (6.44 g, 43.8 mmol) in THF (125 mL) at RT was added DEAD (9.4 mL, 59.7 mmol) over 5 min. After 1 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAc, 2:1) to give the title compound as a white solid (12.6 g, 83%): LCMS (ES) m/z 381 $(M+H)^+$.

d) 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate

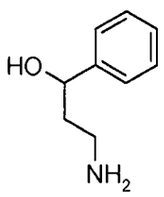
NH_2NH_2 (12.5 mL, 394 mmol) was added to a THF/MeOH (50mL / 50mL) solution of 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate (7.5 g, 19.7 mmol) and stirred at 50 °C in a sealed system. After 12 hours, the solids were filtered, washing with methanol. The filtrate was concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (3.75 g, 76%) as a white solid: LC-MS (ES) m/z = 251 $(M+H)^+$.

Preparation 3



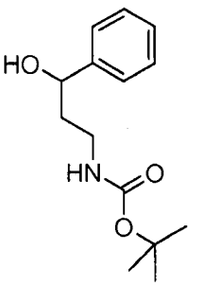
Preparation of 1,1-dimethylethyl (3-amino-3-phenylpropyl)carbamate

a) 3-amino-1-phenyl-1-propanol



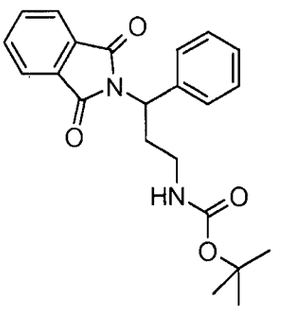
Benzoylacetonitrile (2 g, 13.8 mmol) in THF (35 mL) was added dropwise via addition funnel to a 0 °C solution of LAH (1.6 g, 41.3 mmol) in THF (35 mL). The resulting solution warmed to 25 °C and then was heated to 60 °C for an additional 2h. After cooling to 0 °C, a saturated solution of sodium potassium tartrate was added dropwise and the solution was extracted several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, 5-8% MeOH in DCM (1% NH_4OH)) affording the amino alcohol (1.4 g, 67%) as a clear oil: LCMS (ES) m/z 152 $(M+H)^+$.

b) 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)carbamate



3-amino-1-phenyl-1-propanol (1.4 g, 9.27 mmol) was dissolved in THF (50 mL) and Boc_2O (2.4 g, 11.1 mmol) was added in one portion. After 30 min., the solution was concentrated and the residue purified through via silica (0.5-1% MeOH in DCM (1% NH_4OH)) affording the title compound (1.6 g, 69%) as a pale white solid: LCMS (ES) m/z 152 $(M+H)^+$.

c) 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-phenylpropyl]carbamate



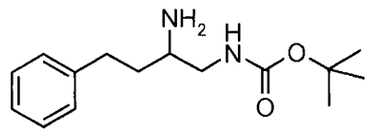
To a solution of 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)carbamate (3 g, 11.95 mmol), PPh_3 (4 g, 15.5 mmol) and phthalimide (1.8 g, 11.95 mmol) in THF (60 mL) at RT was added DEAD (2.4 mL, 15.5 mmol) over 5 min. After 1 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAc, 4:1) to give the title compound as a white solid (2.2 g, 48%): LCMS (ES) m/z 381 $(M+H)^+$.

c) 1,1-dimethylethyl (3-amino-3-phenylpropyl)carbamate

NH_2NH_2 (1.8 mL, 57.7 mmol) was added to a THF/MeOH (1:1, 30 mL) solution of 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-3-phenylpropyl]carbamate (2.2 g, 5.79 mmol) and stirred at 50 °C in a sealed system. After 12 hours, the solids were filtered, washing with methanol. The filtrate was

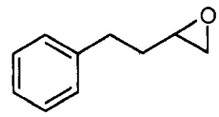
concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 1% NH_4OH to give the title compound (1.1 g, 76%) as a white solid: LC-MS (ES) m/z = 251 $(M+H)^+$.

Preparation 4



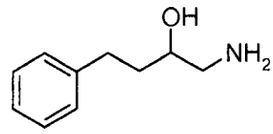
Preparation of 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate

a) 2-(2-phenylethyl)oxirane



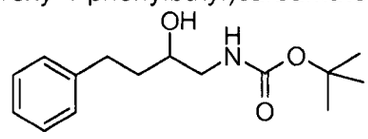
3-chlorobenzenecarboperoxoic acid (12.1 g, 54.0 mmol) is added in one portion to a solution of 3-buten-1-ylbenzene (7.15 g, 54.1 mmol) in CH_2Cl_2 at 0 °C followed by warming to 25 °C overnight. Saturated $NaHCO_3$ was added and the mixture separated and the resulting clear oil (8.0 g, quant.) was carried forward without further purification: LC-MS (ES) m/z = 149 $(M+H)^+$.

b) 1-amino-4-phenyl-2-butanol



2-(2-phenylethyl)oxirane (8.0 g, 54 mmol) was placed in a sealed tube with 7N NH_3-MeOH (130 mL) and stirred 2 hours at 70 °C followed by concentration to a clear oil (and was used without further purification in the following step.

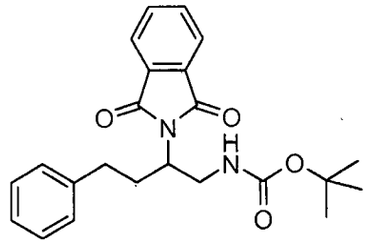
c) 1,1-dimethylethyl (2-hydroxy-4-phenylbutyl)carbamate



1-amino-4-phenyl-2-butanol (7.4 g, 50.0 mmol) was dissolved in THF (50 mL) and Boc_2O (13 g, 59.6 mmol) was added in one portion. After 30 min., the solution was concentrated and the residue purified through a silica plug (5% MeOH

in DCM (0.5% NH_4OH)) affording the title compound (13.1 g, 91%) as a clear yellow oil: LCMS (ES) m/z 266 $(M+H)^+$.

d) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-4-phenylbutyl]carbamate

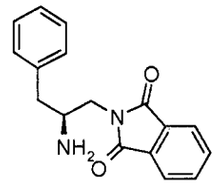


To a solution of 1,1-dimethylethyl (2-hydroxy-4-phenylbutyl)carbamate (3.0 g, 11.4 mmol), PPh_3 (3.6 g, 13.7 mmol) and phthalimide (1.84 g, 12.5 mmol) in THF (60 mL) at RT was added DEAD (1.8 mL, 11.4 mmol) over 5 min. After 0.5 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAC, 2:1) to give the title compound as a white solid (3.1 g, 69%): LCMS (ES) m/z 395 $(M+H)^+$.

e) 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate

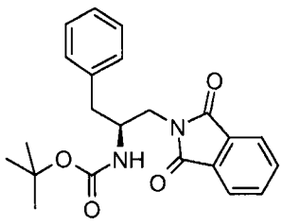
NH_2NH_2 (2.5 mL, 79.6 mmol) was added to a THF/MeOH (40mL/40mL) solution of 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate (3.1 g, 7.83 mmol) and stirred overnight. After 12 hours, the solution was concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (1.4 g, 66%) as a white solid: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparation 5



Preparation of 2-[(2*S*)-2-amino-3-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione

a) 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]carbamate

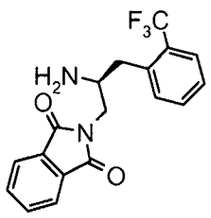


To a solution of (S)-(-)-2-(tert-butoxycarbonylamino)-3-phenyl-1-propanol (3.0 g, 11.9 mmole), PPh_3 (3.74 g, 14.4 mmole) and phthalimide (1.93 g, 13.1 mmole) in THF (75 mL) at RT was added DEAD (2.8 mL, 17.8 mmole) over 5 min. After 1.5 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAC, 2:1) to give the title compound as a white solid (4.3 g, 95%): LCMS (ES) m/z 381 $(M+H)^+$.

b) 2-[(2*S*)-2-amino-3-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione

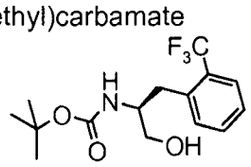
To a solution of 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]carbamate (4.3 g, 11.3 mmole) in MeOH (100 mL) at RT was added 4M HCl in dioxane (50 mL). After stirring for 3h at RT, the reaction solution was concentrated to a white solid (quant.) : LCMS (ES) m/z 281 $(M+H)^+$.

Preparation 6



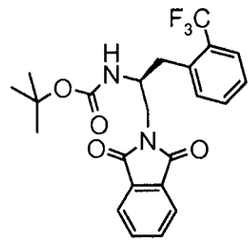
Preparation of 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione

a) 1,1-dimethylethyl ((1S)-2-hydroxy-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate



To a solution of N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine (5 g, 15 mmol) in THF (75 mL) at 0 °C stirred was added BH_3-THF (45 mL, 45 mmol-1M in THF). After 12h, the reaction was quenched with AcOH:MeOH (1:5, 24 mL) and partitioned between saturated aqueous $NaHCO_3$ and DCM. The aqueous phase was then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4 and used directly (4.2 g, 88%): LCMS (ES) m/e 320 $(M+H)^+$.

b) 1,1-dimethylethyl ((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate

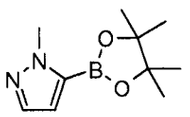


To a solution of 1,1-dimethylethyl ((1S)-2-hydroxy-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate (4.2 g, 13.2 mmol), triphenylphosphine (4.5 g, 17.1 mmol) and phthalimide (1.9 g, 13.2 mmol) in THF (66 mL) at 25 °C was added diethyl azodicarboxylate (2.7 mL, 17.1 mmol). After stirring at RT for 1 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (1 % MeOH in DCM) affording the title compound (3.2 g, 54 %) as a white solid: LCMS (ES) m/z 449 $(M+H)^+$.

c) 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione

To a solution of 1,1-dimethylethyl ((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)carbamate (3.2 g, 7.1 mmol) in MeOH (35 mL) at RT was added 4M HCl in dioxane (18 mL). After 12h, the solution was concentrated affording the title compound (2.7 g, quant.) as the HCl salt: LCMS (ES) m/z 349 $(M+H)^+$.

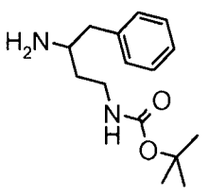
Preparation 7



Preparation of 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole

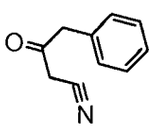
To a solution of 1-methyl pyrazole (4.1 g, 50 mmole) in THF (100 mL) at 0°C was added n-BuLi (2.2M in THF, 55 mmole). The reaction solution was stirred for 1 hour at RT and then cooled to -78°C [*J. Heterocyclic Chem.* 41, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (12.3 mL, 60 mmole). After 15 min at -78°C, the reaction was allowed to warm to 0°C over 1hour. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organic fractions were washed with H_2O (2 x 100 mL), dried over Na_2SO_4 and concentrated under vacuum to afford a tan solid (8.0 g, 77%) which was used without further purification. LCMS (ES) m/z 127 $(M+H)^+$ for $[RB(OH)_2]$; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.57 (s, 1H), 6.75 (s, 1H), 4.16 (s, 3H), and 1.41 (s, 12H).

Preparation 8



Preparation of 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate

a) 3-oxo-4-phenylbutanenitrile



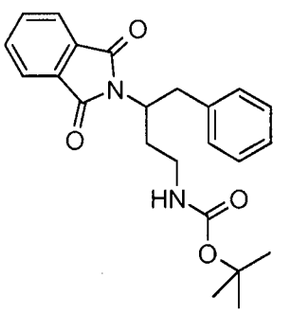
To a solution of cyanoacetic acid (2 g, 23.5 mmol) in THF (100 mL) at -78 °C was added nBuLi (10 mL, 25.9 mmol, 2.5M in hexanes). After 30min, phenylacetyl chloride (1.6 mL, 11.8 mmol) was added dropwise. Following an additional 30min, the solution was partitioned between 1N HCl-Et_2O and the aqueous phase was washed several times with Et_2O. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column

chromatography (silica, 30% EtOAc in hexanes) yielding the title compound (770 mg, 40%) as a tan oil: LCMS (ES) m/z 160 $(M+H)^+$.

b) 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate

A solution of 3-oxo-4-phenylbutanenitrile (1.1 g, 6.92 mmol) in THF (10 mL) was added to a 0 °C solution of lithium aluminum hydride (787 mg, 20.8 mmol) in THF (25 mL). After 12h, the solution was quenched with H_2O (943 uL), 6N NaOH (716 uL) and H_2O (3.5 mL). The resulting precipitate was filtered and the pad was washed several times with DCM. The filtrate was concentrated then redissolved in THF (30 mL) and Boc_2O (1.5 g, 6.92 mmol) was added in one portion. After 30 min, the solution was concentrated and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound (1g, 55%-2steps) as an orange solid: LCMS (ES) m/z 265 $(M+H)^+$.

c) 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-4-phenylbutyl]carbamate



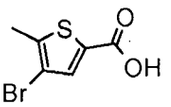
To a solution of 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate (1 g, 3.77 mmol), PPh_3 (1.3 g, 4.91 mmol) and phthalimide (555 mg, 3.77 mmol) in THF (18 mL) at RT was added DEAD (772 uL, 4.91 mmol) over 5 min. After 1 h at RT, the reaction solution was concentrated and purified on silica (hexanes/EtOAc, 5:1) to give the title compound as a white solid (725 mg, 49%): LCMS (ES) m/z 395 $(M+H)^+$.

d) 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate

NH_2NH_2 (577 uL, 18.4 mmol) was added to a THF/MeOH (1:1, 10 mL) solution of 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-4-

phenylbutyl]carbamate (725 mg, 1.84 mmol) and stirred at 50 °C in a sealed system. After 12 hours, the solids were filtered, washing with methanol. The filtrate was concentrated and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 1% NH_4OH to give the title compound (483 mg, quant.) as a white solid: LC-MS (ES) m/z = 264 $(M+H)^+$.

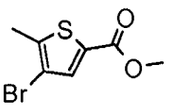
Preparation 9



Preparation of 4-bromo-5-methyl-2-thiophenecarboxylic acid

A solution of bromine (725 uL, 14.1 mmol) in AcOH (2.8 mL) was added dropwise to 5-methyl-2-thiophenecarboxylic acid (2 g, 14.1 mmol) and $FeCl_3$ (456 mg, 2.81 mmol) in AcOH (28 mL) at 25 °C. After 5h, the solution was poured onto ice and the precipitate was filtered and washed with water affording the title compound (3 g, quant.) as a yellow powder: LCMS (ES) m/z 222 $(M+H)^+$.

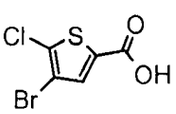
Preparation 10



Preparation of methyl 4-bromo-5-methyl-2-thiophenecarboxylate

A solution of 4-bromo-5-methyl-2-thiophenecarboxylic acid (3 g, 13.6 mmol) in MeOH (67 mL) and H_2SO_4 (3 mL) was stirred at 50 °C. After 12h, the solution was added to ice-H_2O and the pH was adjusted to ~11. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding the title compound (3 g, 94%) as an orange solid: LCMS (ES) m/z 236 (M+H)+.

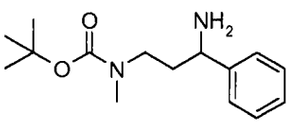
Preparation 11



Preparation of 4-bromo-5-chloro-2-thiophenecarboxylic acid

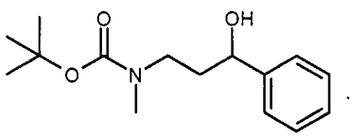
A solution of bromine (634 uL, 12.3 mmol) in AcOH (2.5 mL) was added dropwise to 5-chloro-2-thiophenecarboxylic acid (2 g, 12.3 mmol) and $FeCl_3$ (399 mg, 2.50 mmol) in AcOH (25 mL) at 25 °C. The reaction mixture was warmed to reflux where additional bromine (634 uL, 12.3 mmol) and $FeCl_3$ (399 mg, 2.50 mmol) were added. After 7d, the solution was poured onto ice and the precipitate was filtered and washed with water affording the title compound (3 g, quant.) as a yellow powder: LCMS (ES) m/z 242 $(M+H)^+$.

Preparation 12



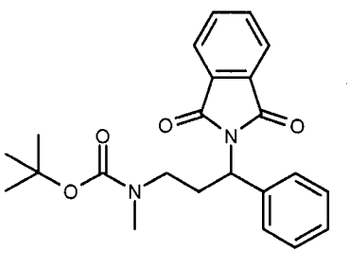
Preparation of 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate

a) 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)methylcarbamate



3-(methylamino)-1-phenyl-1-propanol (4.12 g, 24.9 mmol) was dissolved in THF (30 mL) and Boc_2O (1M/THF, 30 mL, 30 mmol) was added in one portion. After 30 min., the solution was concentrated and the residue purified through a silica plug (5% MeOH in DCM (0.5% NH_4OH)) affording the title compound (6.4 g, 97%) as a clear yellow oil: LCMS (ES) m/z 265 $(M+H)^+$.

b) 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate

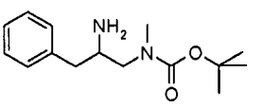


To a solution of 1,1-dimethylethyl (3-hydroxy-3-phenylpropyl)methylcarbamate (2.8 g, 10.4 mmol), PPh_3 (3.3 g, 12.7 mmol) and phthalimide (1.86 g, 12.6 mmol) in THF (50 mL) at RT was added DEAD (1.98 mL, 12.6 mmol) over 5 min. After 0.5 h at RT, MeOH (10 mL) was added and the reaction solution was absorbed onto silica and purified via chromatography (hexanes/EtOAC, 2:1) to give the title compound as a white solid (2.7 g, 65%): LCMS (ES) m/z 395 $(M+H)^+$.

c) 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate

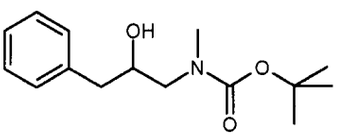
NH_2NH_2 (1.7 mL, 54.2 mmol) was added to a THF/MeOH (50mL/10mL) solution of 1,1-dimethylethyl [3-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate (2.7 g, 6.8 mmol) and stirred overnight. After 12 hours, the solution was absorbed onto silica and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (1.4 mg, 77%) as a white solid: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparation 13



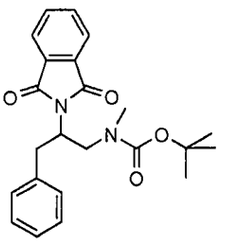
Preparation of 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate

a) 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)methylcarbamate



To a solution of 1-(methylamino)-3-phenyl-2-propanol (13 g, 78 mmol) [prepared according to Galons, H. et al *Eur. J. Med. Chem. Chim. Ther.* **1979** 14, 165-170.] in THF (390 mL) at RT was added $(Boc)_2O$ (21.6 g, 99 mmol). After stirring at RT for 2 h, the reaction solution was absorbed onto silica and purified via chromatography (35% EtOAc/Hex) affording the title compound (11.6 g, 56%) as a clear yellow oil: LCMS (ES) m/z 266 $(M+H)^+$.

b) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate

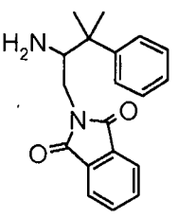


To a solution of 1,1-dimethylethyl (2-hydroxy-3-phenylpropyl)methylcarbamate (11.6 g, 43.72 mmol), PPh_3 (14.3 g, 54.5 mmol) and phthalimide (8.7 g, 59.1mmol) in THF (220 mL) at RT was added DEAD (8.5 mL, 54 mmol) over 15 min. After 0.5 h at RT, MeOH (10 mL) was added and the reaction solution was absorbed onto silica and purified via chromatography (hexanes/EtOAC, 2:1) to give the title compound as a white solid (9.97 g, 57%): LCMS (ES) m/z 395 $(M+H)^+$.

c) 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate

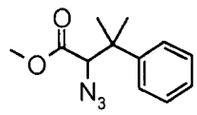
NH_2NH_2 (7 mL, 0.2 mol) was added to a THF/MeOH (100mL/25mL) solution of 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-3-phenylpropyl]methylcarbamate (2.7 g, 6.8 mmol) and stirred overnight. After 12 hours, the solution was absorbed onto silica and purified by column chromatography using 5% MeOH in $CHCl_3$ containing 0.5% NH_4OH to give the title compound (5.8 mg, 88%) as a white solid: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparation 14



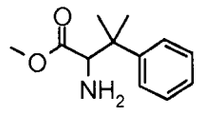
Preparation of 2-(2-amino-3-methyl-3-phenylbutyl)-1H-isoindole-1,3(2H)-dione

a) methyl 2-azido-3-methyl-3-phenylbutanoate



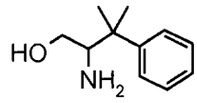
To a solution of KHMDS (36 mL, 17.9 mmol) in THF (70 mL) at -78 °C was added methyl 3-methyl-3-phenylbutanoate (3 g, 15.6 mmol) in THF (15 mL) dropwise. After 1h, trisylazide (5 g, 18.7 mmol) in THF (15 mL) was added dropwise over 10 min. After an additional 5 min, acetic acid (4.1 mL) was added and the reaction mixture warmed to 25 °C over 1h. The solution was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 20% EtOAc in hexanes) yielding the title compound (2.6 g, 71%) contaminated with 33% methyl 3-methyl-3-phenylbutanoate to be purified out in the following steps: LCMS (ES) m/e 234 $(M+H)^+$.

b) methyl beta,beta-dimethylphenylalaninate



A solution of methyl 2-azido-3-methyl-3-phenylbutanoate (2.6 g, 11.2 mmol) and PPh_3 (4.4 g, 16.7 mmol) in H_2O (400 uL) and THF (100 mL) was stirred at 25 °C over 2d then at 50 °C for 12h. The solution was concentrated and purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)) yielding the title compound (1.4 g, quant.): LCMS (ES) m/e 208 $(M+H)^+$.

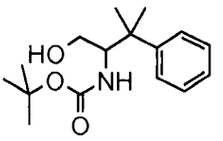
c) 2-amino-3-methyl-3-phenyl-1-butanol



To a solution of methyl beta,beta-dimethylphenylalaninate (1.4 g, 6.76 mmol) in THF (20 mL) at 0 °C was added dropwise a solution of lithium aluminum hydride (384 mg, 10.1 mmol) in THF (10 mL). After warming to 25 °C over 12h, the solution was quenched by sequential addition of H_2O (659 uL), 6N NaOH (500 uL) and H_2O (2.4 mL). The resulting precipitate was filtered and the pad washed thoroughly with DCM. The filtrate was concentrated and purified via column

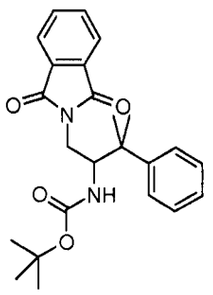
chromatography (silica, 2-5% MeOH in DCM (1% NH_4OH)) yielding the title compound (770 mg, 64%): LCMS (ES) m/e 179 $(M+H)^+$.

d) 1,1-dimethylethyl [1-(hydroxymethyl)-2-methyl-2-phenylpropyl]carbamate



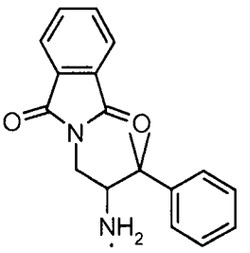
Boc_2O (1 g, 4.76 mmol) was added in one portion to 2-amino-3-methyl-3-phenyl-1-butanol (770 mg, 4.33 mmol) in THF (20 mL) at 25 °C. After 30 min, the solution was concentrated yielding the title compound (1.2 g, quant.) as a white solid which was used without further purification: LCMS (ES) m/e 279 (M+H)+.

e) 1,1-dimethylethyl {1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-2-methyl-2-phenylpropyl}carbamate



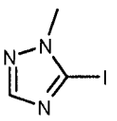
To a solution of 1,1-dimethylethyl [1-(hydroxymethyl)-2-methyl-2-phenylpropyl]carbamate (775 mg, 2.8 mmol), triphenylphosphine (915 mg, 3.5 mmol) and phthalimide (499 mg, 3.4 mmol) in THF (15 mL) at 25 °C was added diethyl azodicarboxylate (0.54 mL, 3.4 mmol). After stirring at RT for 1 h, MeOH was added (5 mL) and the solution was adsorbed onto silica and purified via column chromatography (1 % MeOH in DCM) affording the title compound (723 mg, 64 %) as a white solid: LCMS (ES) m/z 409 $(M+H)^+$.

f) 2-(2-amino-3-methyl-3-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione



To a solution of 1,1-dimethylethyl {1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-2-methyl-2-phenylpropyl}carbamate (723 mg, 1.77 mmol) in $CHCl_3$:MeOH (10:1, 55 mL) at RT was added 4M HCl in dioxane (10 mL). After stirring for 3h at RT, the reaction solution was concentrated to a white solid (quant.): LCMS (ES) m/z 309 $(M+H)^+$.

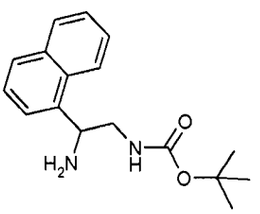
Preparation 15



Preparation of 5-iodo-1-methyl-1*H*-1,2,4-triazole

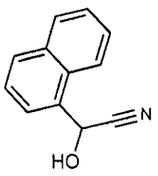
1-methyl-1*H*-1,2,4-triazole (2.05 g, 24.7 mmol) was added slowly over 15 minutes to an Et_2O solution of nBuLi at -70 °C. The mixture was stirred for 60 minutes at -70 °C and allowed to warm to -30 °C. A solution of I_2 (6.5 g, 25.6 mmol) in THF (27 mL) was added slowly over 15 minutes and the mixture was allowed to warm to room temperature and stir for 60 minutes. The mixture was partitioned with saturated $Na_2S_2O_3$, the phases were separated and the organic solvent removed. The crude iodide was used without further purification: LCMS (ES) m/z 210 $(M+H)^+$.

Preparation 16



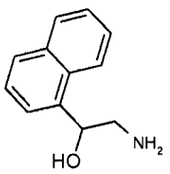
Preparation of 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate

a) hydroxy(1-naphthalenyl)acetonitrile



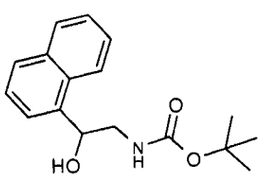
To a solution of potassium cyanide in ether (100 mL) at 0 °C was added dropwise a mixture of 1-naphthalenecarbaldehyde (1.56 g, 10 mmol) and acetic acid (1.41g, 23.5 mmol) in ether (10 mL). The resulting mixture was warmed to 25 °C. for 20h, where the precipitate was filtered and the filtrate was concentrated affording the title compound as a clear oil (1.67 g, 9.14 mmol, 91%): LCMS (ES) m/z 184 $(M+H)^+$.

b) 2-amino-1-(1-naphthalenyl)ethanol



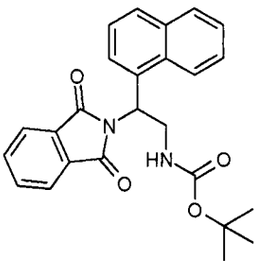
To a solution of hydroxy(1-naphthalenyl)acetonitrile (1.67 g, 9.14 mol) in THF (90 mL) at 0 °C was added dropwise a solution of LAH-THF (1M, 11 mL, 11 mmol). After 2 hrs, the solution was quenched by sequential addition of H_2O (0.42 mL), 6N NaOH (6M, 0.32 mL) and H_2O (1.6 mL). The resulting precipitate was filtered and the filtrate was concentrated and used directly yielding the title compound (0.897 g, 4.8 mmol, 53%) as a clear oil: LCMS (ES) m/z 188 $(M+H)^+$.

c). 1,1-dimethylethyl [2-hydroxy-2-(1-naphthalenyl)ethyl]carbamate



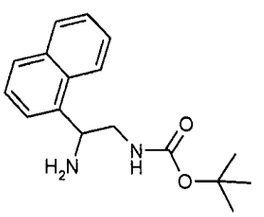
To a solution of 2-amino-1-(1-naphthalenyl)ethanol(1.38g, 4.8 mmol) in dichloromethane (50 mL) was added Boc anhydride (1.155 g, 5.3 mmole). After stirring at RT for 12 h, the reaction solution was concentrated and partitioned between $NaHCO_3$ sat./DCM. The aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding the title compound as a white solid (1.378 g, 4.8 mmol, quant): LCMS (ES) m/z 288 (M+H)+.

d) 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-(1-naphthalenyl)ethyl]carbamate



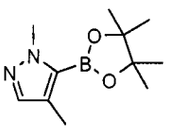
To a solution of 1,1-dimethylethyl [2-hydroxy-2-(1-naphthalenyl)ethyl]carbamate (1.38 g, 4.8 mmol), triphenylphosphine (1.52 g, 5.76 mmol) and phthalimide (0.74 g, 5.04 mmol) in THF (50 mL) at 25 °C was added diethyl azodicarboxylate (0.87 mL, 5.52 mmol). After stirring at RT for 1 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (20% EtOAc in hexanes) affording the title compound (1.29 g, 3.1 mmol, 65 %) as a white solid: LCMS (ES) m/z 387 (M+H)+.

e) 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate



To a solution of 1,1-dimethylethyl [2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-2-(1-naphthalenyl)ethyl]carbamate (1.29 g, 3.1 mmol) in MeOH (30 mL) was added anhydrous hydrazine (0.5 mL, 15.5 mmol) at 25 °C. After 12h, the solution was partitioned between DCM/H_2O. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding the title compound as a white solid (491 mg, 1.72 mmole, 55%): LCMS (ES) m/z 287 $(M+H)^+$.

Preparation 17

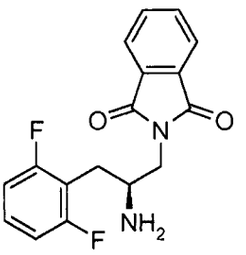


Preparation of 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

To a suspension of NaH (60% in mineral oil, 3.5 g, 146 mmol, washed with 200 mL of hexane) in THF (200 mL) was added 4-methyl-1H-pyrazole (10 g, 122 mmol) at 0 °C dropwise. After stirring at RT for 1h, to above suspension was added MeI (7.3 mL, 117 mmol) dropwise at 0 °C. The reaction mixture was stirred overnight. The NaI by-product was removed by filtration and the filtrate solution was used directly in the next step.

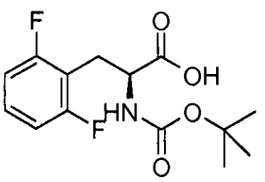
At 0°C, to above THF solution of 1,4-dimethyl pyrazole was added n-BuLi (2.5M in hexane, 58.5 mL, 146 mmole). The reaction solution was stirred for 2 hour at RT and then cooled to -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (27.2 g, 146 mmole). After 15 min at -78°C, the reaction was allowed to warm to 0°C and stir for 3h. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown solid (21 g, 78%) which was used directly without further purification: LC-MS: 141 $(M-C_6H_{12})^+$, 223 $(M+H)^+$. ^1H NMR ($CDCl_3$): δ 7.28 (s, 1H), 4.03 (s, 3H), 2.22 (s, 3H), and 1.32 (s, 12H).

Preparation 18



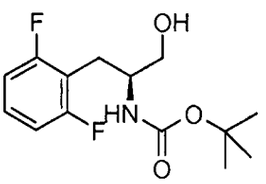
Preparation of 2-[(2*S*)-2-amino-3-(2,6-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

a) *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-2,6-difluoro-L-phenylalanine



1,4-Dioxane (55 mL) and water (12 mL) was added to 2,6-difluoro-L-phenylalanine (3.00 g, 12.62 mmol) in a 200 mL round-bottomed flask. The mixture was cooled to 0 °C followed by the slow addition of NaOH (12.62 mL, 31.6 mmol) and then Boc_2O (3.42 g, 15.20 mmol). The mixture was allowed to warm to room temperature and monitored for completion by LC-MS. Upon completion, the mixture was cooled to 0 °C and made neutral by the slow addition of 2.5M HCl (12 mL). The solvents removed under reduced pressure. The resulting solid was sonicated with 20%MeOH/$CHCl_3$ (150mL), filtered and the organic solvent removed to give the product (4.3 g, 14.4 mmol, quant.) as a white solid which was used in the next step without further purification: LC-MS (ES) m/z = 302 $(M+H)^+$.

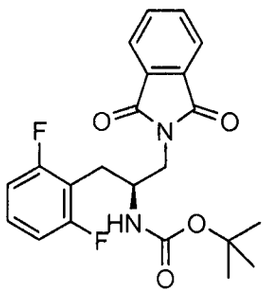
b) 1,1-dimethylethyl [(1*S*)-2-(2,6-difluorophenyl)-1-(hydroxymethyl)ethyl]carbamate



BH_3.THF (64.7 ml, 64.7 mmol) was added slowly to a tetrahydrofuran (THF) (60 mL) solution of N-{[(1,1-dimethylethyl)oxy]carbonyl}-2,6-difluoro-L-phenylalanine (4.33 g, 14.37 mmol) at 0 °C in a 200 mL round-bottomed flask. The

mixture was stirred for 2 hours and then placed in the freezer overnight. Excess reagent was quenched by the slow addition of AcOH in MeOH at 0 °C and the mixture warmed to room temperature for 2 hours. The THF volume was reduced by 1/2 and the product partitioned between $CHCl_3$ and aqueous $NaHCO_{3\ (sat)}$. The combined organic fractions were dried over Na_2SO_4 and used directly without further purification (3.4 g, 78%): LC-MS (ES) m/z = 288 $(M+H)^+$.

c) 1,1-dimethylethyl {(1*S*)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}carbamate

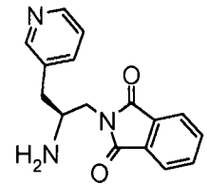


To a 200 mL round-bottomed flask was added 1,1-dimethylethyl [(1S)-2-(2,6-difluorophenyl)-1-(hydroxymethyl)ethyl]carbamate (3.38 g, 11.76 mmol), phthalimide (2.02 g, 13.73 mmol), and PS – TPP (Polymer bound TriphenylPhosphine (2.15 mmol/g, 4.92 g, 14.76 mmol) in Tetrahydrofuran (THF) (58.8 ml). DEAD (2.23 ml, 14.09 mmol) was added and the mixture stirred at ambient temperature for approximately 30 minutes at which point MeOH was added. The mixture was filtered through Celite adsorbed onto silica and purified via column chromatography affording the title compound (2.7 g, 55%): LC-MS (ES) m/z = 317 $(M+H)^+$.

d) 2-[(2*S*)-2-amino-3-(2,6-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

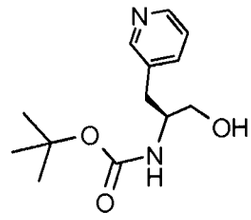
In a 200 mL round-bottomed flask was added 1,1-dimethylethyl {(1S)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}carbamate (2.72 g, 6.40 mmol) in Chloroform (75 ml) and Methanol (10 ml). HCl / 1,4-Dioxane (40.0 ml, 160 mmol) was added and the mixture stirred overnight. The solvents were removed affording the title compound (2.4 g, quant.) as the HCl salt: LC-MS (ES) m/z = 317 $(M+H)^+$.

Preparation 19



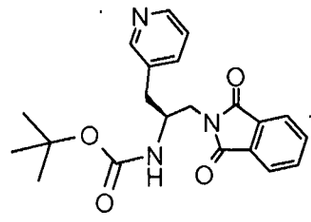
Preparation of 2-[(2*S*)-2-amino-3-(3-pyridinyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

a) 1,1-dimethylethyl [(1*S*)-2-hydroxy-1-(3-pyridinylmethyl)ethyl]carbamate



To a solution of Boc-L-3-pyridylaniline (1.064 g, 4 mmol) in THF (5 mL) at 0 °C was added BH_3-THF (20 mL, 20 mmol-1M in THF) dropwise. After 2 h, the reaction was quenched with AcOH:MeOH (1:5, 14.3 mL) at 0 °C, followed by Et_3N (1.67 mL, 12 mmol) and I_2 (2.03 g, 8 mmol). The resulting mixture was warmed to ambient temperature and stirred for 20h, turning from brown to colorless. The solution was concentrated and partitioned between DCM and water. The aqueous phase was then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated to afford the desired product as a colorless oil which was used without further purification (957.6 mg, 95%): LC-MS (ES) m/z= 253 $(M+H)^+$.

b) 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(3-pyridinylmethyl)ethyl]carbamate



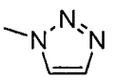
To a solution of 1,1-dimethylethyl [(1*S*)-2-hydroxy-1-(3-pyridinylmethyl)ethyl]carbamate (958 mg, 3.8 mmol), triphenylphosphine (1.21 g,

4.6 mmol) and phthalimide (617 mg, 4.2 mmol) in THF (40 mL) at 25 °C was added diethyl azodicarboxylate (0.72 mL, 4.6 mmol). After stirring at RT for 1 h, the reaction solution was concentrated under vacuum and the residue purified on silica gel (0-50% ethyl acetate / hexane) affording the title compound (797 mg, 55 %) as a white solid: LCMS (ES) m/z 382 $(M+H)^+$.

c) 2-[(2*S*)-2-amino-3-(3-pyridinyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione

To a solution of 1,1-dimethylethyl [(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(3-pyridinylmethyl)ethyl]carbamate (796.7 mg, 2.1 mmol) in DCM (10 mL) at RT was added 1M HCl in dioxane (10 mL). After 20h, the solution was concentrated affording the title compound (404 mg, 68%) as the HCl salt: LCMS (ES) m/z 282 $(M+H)^+$.

Preparation 20

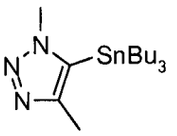


Preparation of 1-methyl-1*H*-1,2,3-triazole

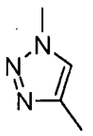
To a solution of 1,2,3-trazole (10 g, 145 mmol) in 150 ml of THF were added potassium carbonate (40 g, 290 mmol) and MeI (13.58 ml, 217 mmol). The resulting reaction mixture was stirred at rt for 3hr. The reaction mixture was filtered and the filtrate was concentrated to afford the title compound (9.2 g, 78%). 1H NMR (400 MHz, $CDCl_3$) δppm 7.71 (s, 1H), 7.55 (s, 1H), 4.14 (s, 3H).

Preparation 21

Preparation of 1,4-dimethyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole

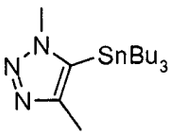


a) 1,4-dimethyl-1*H*-1,2,3-triazole



A solution of methylamine (25.4 ml, 50.8 mmol, 2M in MeOH) was added dropwise to a suspension of N'-(2,2-dichloro-1-methylethylidene)-4-methylbenzenesulfonohydrazide (ref: Sakai, K. et al, *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 179-183) (3 g, 10.16 mmol) in methanol (10 ml) at 0 °C. The solid went into solution. The resulting dark brown mixture was stirred at 0 °C for 2h, evaporated, and the solid was filtered and rinsed with EtOAc. The combined filtrates were concentrated and purified on a 25M biotage column, which was eluted with 50-75% of EA/hexane to give 0.57 g of brown liquid. LC-MS (ES) m/z = 98 $(M+H)^+$, ^1H NMR ($CDCl_3$, 400 MHz) δ 7.27 (s, 1H), 4.06 (s, 3H), 2.35 (s, 3H).

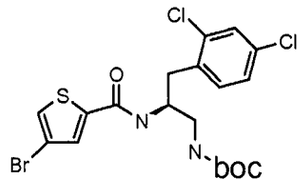
b) 1,4-dimethyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole



A solution of 1,4-dimethyl-1,2,3-triazole (0.56 g, 5.77 mmol) in THF (5 mL) was added dropwise to a solution of BuLi (2.77 ml, 6.92 mmol, 2.5 M in hexane) in 30 mL of THF at -78 °C under N_2. The resulting cloudy mixture was stirred at -70 °C for 1h.

Then tributyltinchloride (1.711 ml, 6.34 mmol) was added. The reaction mixture became clear and was stirred at this temperature for 30 min, and gradually warmed to rt. To the reaction mixture was added 10 ml of NH_4Cl and 10 ml of water. The reaction mixture was extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on FCC (20% EA/Hexane) to give 1.7 g of a clear liquid (73%). LC-MS (ES) m/z = 388 $(M+H)^+$, ^1H NMR ($CDCl_3$, 400 MHz) δ 4.05 (s, 3H), 2.38 (s, 3H), 1.5-0.9 (m, 27H)

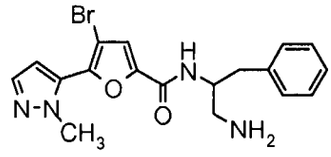
Preparation 22



Preparation of 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(2,4-dichlorophenyl)propyl]carbamate

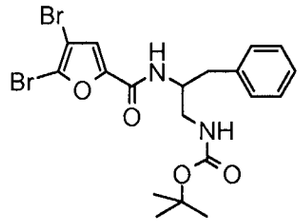
A solution of 4-bromo-2-thiophenecarboxylic acid (1.29 g, 6.22 mmol), 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (2.0 g, 5.19 mmol), PyBrop (3.62 g, 7.78 mmol) and Hunig's Base (3.62 ml, 20.74 mmol) in DCM (50 ml) was stirred at RT for 30 min. The reaction mixture was washed with H_2O, 1N HCl, $NaHCO_3$ (sat. aq.) and brine. The solvent was removed and the residue was dissolved in MeOH, hydrazine monohydrate (1.3 g, 26 mmol) was added. The reaction was stirred at rt overnight. The white solid formed, and was filtered and rinsed with DCM. To the filtrates were added $(Boc)_2O$ (1.7g, 7.78 mmol) and $NaHCO_3$ (sat. aq., 3 ml). The reaction mixture was stirred at RT for 2 hours and was washed with $NaHCO_3$ (sat. aq.) and brine. The solvent was removed and the residue was purified by biotage (50% H/E) to give the product (2.0g, 76%). LC-MS (ES) m/z = 531.0 $(M+Na)^+$.

Example 1



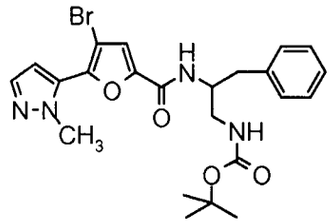
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

a) 1,1-dimethylethyl (2-{[(4,5-dibromo-2-furanyl)carbonyl]amino}-3-phenylpropyl)carbamate



To a solution of 4,5-dibromo-2-furancarboxylic acid (2.81 g, 10.4 mmol), PyBrOP (5.6 g, 12.0 mmol) and diisopropylethyl amine (4.2 mL, 24.0 mmol) in DCM (70 mL) at 25 °C was added 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (2.0 g, 8.0 mmol). After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, hexanes/EtOAc, 2:1) affording the title compound (4.3 g, 82%) as a white solid: LC-MS (ES) m/z = 503 $(M+H)^+$.

b) 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate



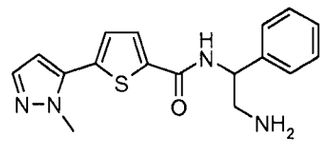
To a solution of 1,1-dimethylethyl (2-{[(4,5-dibromo-2-furanyl)carbonyl]amino}-3-phenylpropyl)carbamate (0.30 g, 0.60 mmol) in dioxane/H_2O (5:1, 8.6 mL) was added K_2CO_3 (0.25 g, 1.8 mmol), tetrakistriphenylphosphine Pd(0) (70 mg, 0.06 mmol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (0.12 g, 0.60 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h. The reaction solution was poured onto H_2O (100 mL) and extracted with DCM. The organics were dried (Na_2SO_4), concentrated under vacuum, and purified on silica gel (hexanes/EtOAc, 1:1) to give the title compound (0.20 g, 66%) as a white solid: LC-MS (ES) m/z = 504.

c) *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

1,1-Dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate (0.20 g, 0.40 mmol) was dissolved in DCM (10 mL) and treated with TFA (5 mL). After 2 h, the solution was

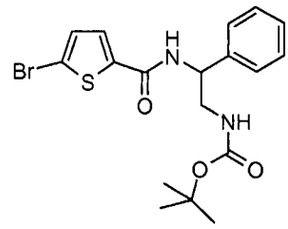
concentrated, and purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt of the title compound (0.16 g, 91%) as a white powder: LC-MS (ES) m/z = 405 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.59 (s, 1H), 7.33 (m, 3H), 7.30 (m, 2H), 6.85 (s, 1H), 4.57 (m, 1H), 4.03 (s, 3H), 3.25 (m, 1H), 3.14 (m, 1H), and 2.98 (m, 2H).

Example 2



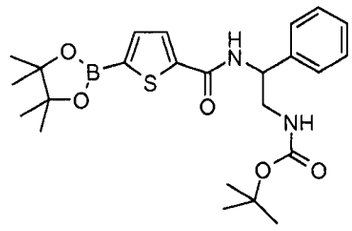
Preparation of *N*-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-2-phenylethyl)carbamate



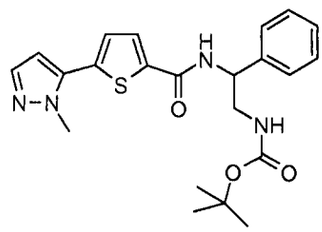
To a solution of 5-bromo-2-thiophenecarboxylic acid (3.2 g, 15.2 mmol), PyBrOP (8.5 g, 18.2 mmol) and diisopropylethyl amine (10.6 mL, 60.9 mmol) in DCM (76 mL) at 25 °C was added 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate (3.6 g, 3.14 mmol)[prepared in Preparation 1]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fraction were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, 1% MeOH in DCM) affording the title compound (4 g, 62%) as a white solid: LC-MS (ES) m/z = 426 $(M+H)^+$.

b) 1,1-dimethylethyl [2-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)ethyl]carbamate



To a solution of 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-2-phenylethyl)carbamate (1 g, 2.35 mmol) in DMF (9 mL) were added KOAc (693 mg, 7.05 mmol), bis(pinocolato)diboron (1.2 g, 4.71 mmol) and $Pd(dppf)Cl_2$ (169 mg, 0.212 mmol). The reaction contents were heated to 80°C in a sealed tube for 18 hours and were then partitioned between 6N NaOH and DCM. The pH of the aqueous fraction was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated to a solid under vacuum and used directly in the next reaction: LC-MS (ES) m/z = 473 $(M+H)^+$ boronic ester, 391$(M+H)^+$ boronic acid.

c) 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate

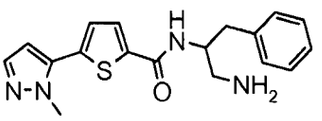


To a solution of 1,1-dimethylethyl [2-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)ethyl]carbamate (200 mg, 0.42 mmol) in dioxane/H_2O (5:1, 8.6 mL) was added K_2CO_3 (234 mg, 1.69 mmol), tetrakistriphenylphosphine Pd(0) (24 mg, 0.02 mmol), and 5-iodo-1-methyl-1H-pyrazole (97 mg, 0.47 mmol) [prepared according to Effenberger, F.; et al *J. Org. Chem.* **1984**, 49, 24, 4687]. The reaction mixture was heated to 80° C in a sealed tube for 12h. The reaction solution was poured onto H_2O (100 mL) and extracted with DCM. The organics were dried (Na_2SO_4), concentrated under vacuum, and purified on silica gel (1% MeOH in DCM) to give the title compound (56 mg, 31%) as a yellow solid: LC-MS (ES) m/z = 427.

d) *N*-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (56 mg, 0.131 mmol) was dissolved in MeOH (2 mL) and treated with excess 4M HCl in dioxane (656 μL, 2.62 mmol). After 4h, the solution was concentrated affording the title compound (46 mg, quant.) as a yellow solid: LC-MS (ES) m/z 327 $(M+H)^+$, ^{1}H NMR (d6-DMSO, 400 MHz) δ 9.46 (d, J = 8.2 Hz, 1H), 8.27 (bs, 1H), 8.20 (d, J = 4.0 Hz, 1H), 7.48-7.75 (m, 3H), 7.37-7.40 (m, 2H), 7.31-7.33 (m, 1H), 6.58 (d, J = 1.9 Hz, 1H), 5.21-5.30 (m, 1H), 3.97 (s, 3H), 3.36-3.41 (m, 1H), 3.19-3.25 (m, 1H).

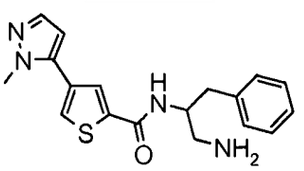
Example 3



Preparation of N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an tan solid according to Example 2, except substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (1.65 g, 7.97 mmol)[prepared in Preparation 2] for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate: LC-MS (ES) m/z 341 $(M+H)^+$, ^{1}H NMR (d_6-DMSO, 400 MHz) δ 8.74 (d, J = 8.5 Hz, 1H), 8.05 (bs, 1H), 7.89 (d, J = 3.9 Hz, 1H), 7.47 (d, J = 1.9 Hz, 1H), 7.43 (d, J = 3.9 Hz, 1H), 7.26-7.29 (m, 3H), 7.20-7.22 (m, 1H), 6.56 (d, J = 2.0 Hz, 1H), 4.31-4.42 (m, 1H), 2.98-3.01 (m, 2H), 2.91-2.93 (m, 2H).

Example 4

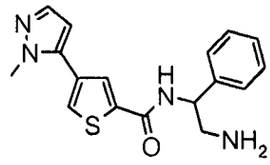


Preparation of N-[2-amino-1-(phenylmethyl)ethyl]-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 2, except substituting 4-bromo-2-thiophenecarboxylic acid (1 g, 4.83 mmol) for 5-bromo-2-thiophenecarboxylic acid and 1,1-dimethylethyl (2-amino-3-

phenylpropyl)carbamate (1.2 g, 4.83 mmol)[prepared in Preparation 2] for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate: LC-MS (ES) m/z 441 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 8.98 (bs, 1H), 8.29 (s, 1H), 8.17 (bs, 2H), 7.98 (s, 1H), 7.46 (s, 1H), 7.27-7.29 (m, 3H), 7.19 (s, 1H), 6.46 (s, 1H), 4.35-4.37 (m, 1H), 3.51 (s, 3H), 2.75-3.12 (m, 4H).

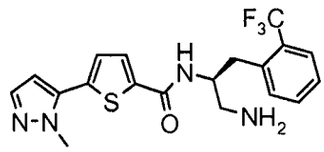
Example 5



Preparation of N-(2-amino-1-phenylethyl)-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide

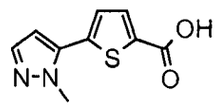
The title compound was prepared as a yellow solid according to Example 2, except substituting 4-bromo-2-thiophenecarboxylic acid (650 mg, 3.14 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 427 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 9.65 (d, J = 7.3 Hz, 1H), 8.58 (s, 1H), 8.31 (br s, 2H), 7.99 (s, 1H), 7.42-7.51 (m, 2H), 7.72-7.80 (m, 2H), 7.20-7.31 (m, 1H), 6.51 (s, 1H), 3.52 (s, 1H), 5.25-5.35 (m, 1H), 3.51 (s, 3H), 3.32-3.48 (m, 1H), 3.15-3.21 (m, 1H).

Example 6



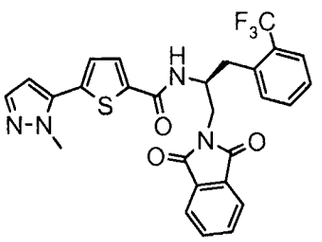
Preparation of N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 5-bromo-2-thiophenecarboxylic acid (100 mg, 0.48 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (267 mg, 1.93 mmol), tetrakistriphenylphosphine Pd(0) (28 mg, 24 umol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (94 mg, 0.48 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h and was then partitioned between 6N NaOH and DCM. The pH of the aqueous phase was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (~100 mg, quant.): LC-MS (ES) m/z = 209 $(M+H)^+$.

b) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (100 mg, 0.48 mmol), PyBrOP (270 mg, 0.58 mmol) and diisopropylethyl amine (420 µL, 2.4 mmol) in DCM (5 mL) at 25 °C was added 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (168 mg, 0.48 mmol)[from Preparation 6]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica) affording the title compound (74 mg, 28%) as a white solid: LC-MS (ES) m/z = 539 $(M+H)^+$.

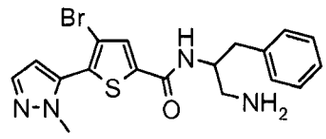
c) N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (74 mg, 0.14 mmol) in MeOH/THF (2 mL, 1:1) at RT was added hydrazine (86 µL, 2.75 mmol). After stirring for 18h at RT, the reaction

solution was concentrated under vacuum and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound.

The neutral compound from above was dissolved in MeOH (2 mL), treated with excess 4M HCl in dioxane (500 μL) and concentrated affording the HCl salt of the title compound: LC-MS (ES) m/z = 409 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 8.97 (d, J = 9.0 Hz, 1H), 8.17 (bs, 1H), 8.00 (d, 3.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.55-7.61 (m, 2H), 7.42-7.47 (m 2H), 6.56 (d, J = 2.0 Hz, 1H), 4.47-4.51 (m, 1H), 4.18 (s, 3H), 3.09-3.11 (m, 4H).

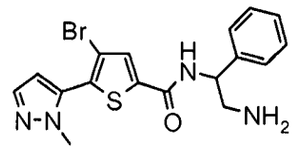
Example 7



Preparation of N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 1, except substituting 4,5-dibromo thiophenecarboxylic acid (376 mg, 1.32 mmol) for 4,5-dibromo furancarboxylic acid: LC-MS (ES) m/z = 419 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 8.92 (d, J = 8.6 Hz, 1H), 8.03-8.06 (m, 2H), 7.56 (d, J = 1.9 Hz, 1H), 7.26-7.32 (m, 3H), 7.21-7.23 (m, 1H), 6.55 (d, J = 1.9 Hz, 1H), 4.32-4.42 (m, 1H), 3.77 (s, 3H), 3.00-3.01 (m, 2H), 2.89-2.91 (m, 2H).

Example 8

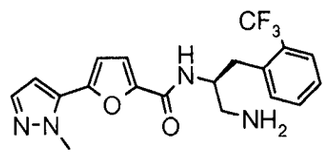


Preparation of N-(2-amino-1-phenylethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 1, except substituting 4,5-dibromo thiophenecarboxylic acid (2.2 g, 7.69 mmol) for

4,5-dibromo furancarboxylic acid and 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate (1.1 g, 4.66 mmol) for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate: LC-MS (ES) m/z = 406 $(M+H)^+$, ^1H NMR (d6-DMSO, 400 MHz) δ 9.47 (d, J = 7.9 Hz, 1H), 8.26 (s, 1H), 8.17 (bs, 1H), 7.58 (d, J = 1.6 Hz, 1H), 7.38-7.46 (m, 3H), 7.30-7.34 (m, 1H), 6.56 (d, J = 1.6 Hz, 1H), 5.28-5.37 (m, 1H), 3.81 (s, 3H), 3.35-3.41 (m, 1H), 3.21-3.28 (m, 1H).

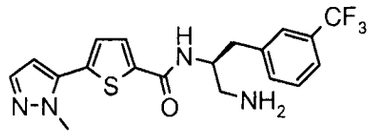
Example 9



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 5-bromo-2-furancarboxylic acid (58 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.62 (br s, 1H), 7.57 (m, 1H), 7.51 (m, 3H), 7.22 (m, 1H), 6.91 (m, 1H), 6.76 (m, 1H), 4.6 (m, 1H), 4.07 (m, 3H) and 3.15 (m, 4H).

Example 10

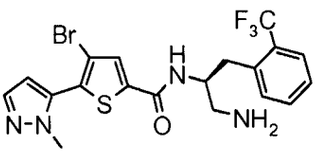


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (306 mg, 0.80 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-

HCl: LC-MS (ES) m/z = 409 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 2.81 - 2.88 (m, 1H) 2.93 (td, *J*= 9.03, 4.93 Hz, 2H) 3.09 (dd, *J*= 13.89, 5.31 Hz, 1H) 4.00 (s, 3H) 4.28 - 4.35 (m, 1H) 6.53 (d, *J*= 2.02 Hz, 1 H) 7.32 (d, *J*= 4.04 Hz, 1H) 7.45 - 7.52 (m, 3H) 7.54 - 7.58 (m, 1H) 7.60 (s, 1H) 7.70 (d, *J*= 4.04 Hz, 1H).

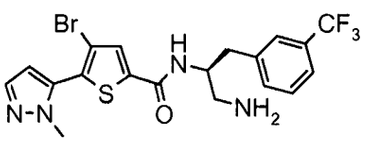
Example 11



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (237 mg, 0.83 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z = 488 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δppm 2.97 - 3.10 (m, 4H) 3.78 (s, 3H) 4.42 - 4.54 (m, 1H) 6.56 (d, *J*=2.02 Hz, 1H) 7.45 (t, *J*=7.58 Hz, 1H) 7.50 - 7.54 (m, 1H) 7.56 - 7.63 (m, 2H) 7.71 (d, *J*=7.58 Hz, 1H) 7.92 (s, 1H) 8.76 (d, *J*=9.09 Hz, 1H)

Example 12

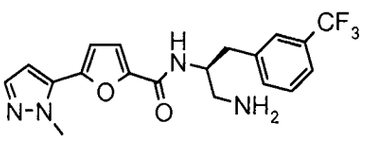


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (237 mg, 0.83 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (206 mg, 0.535 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-

isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 488 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 2.97 - 3.07 (m, 1H) 3.10 - 3.21 (m, 2H) 3.27 (d, *J*=3.54 Hz, 1H) 3.82 (s, 3H) 4.50 - 4.59 (m, 1H) 6.51 (d, *J*= 2.02 Hz, 1H) 7.50 - 7.60 (m, 4H) 7.62 (s, 1H) 7.71 (s, 1H).

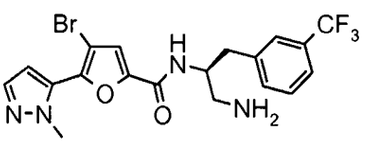
Example 13



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 5-bromo-2-furancarboxylic acid (44 mg, 0.23 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (87 mg, 0.25 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.63 (br s, 1H), 7.57 (m, 1H), 7.51 (m, 3H), 7.22 (m, 1H), 6.91 (m, 1H), 6.77 (m, 1H), 4.6 (m, 1H), 4.07 (m, 3H) and 3.14 (m, 4H).

Example 14

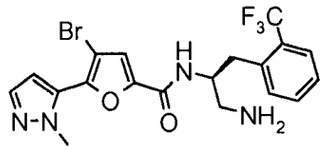


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-furancarboxylic acid (82 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl (115 mg,

0.3 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.61 (m, 2H), 7.53 (m, 3H), 7.30 (m, 1H), 6.84 (m, 1H), 4.59 (m, 1H), 4.03 (s, 3H), 3.28 (m, 1H), 3.17 (m, 2H) and 3.01 (m, 1H)

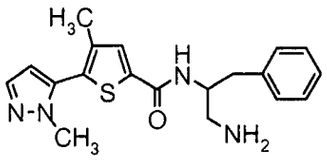
Example 15



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

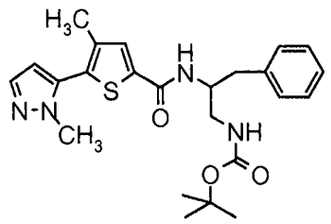
The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-furancarboxylic acid (82 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.71 (m, 1H), 7.60 (m, 1H), 7.53 (m, 2H), 7.44 (m, 1H), 7.33 (m, 1H), 6.88 (m, 1H), 4.7 (m, 1H), 4.06 (s, 3H), 3.25 (m, 3H) and 3.09 (m, 1H).

Example 16



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

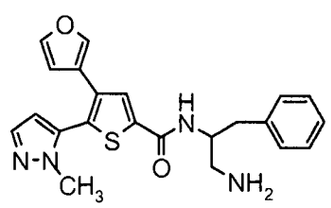


To a solution of 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (0.35 g, 0.67 mmol) [from Example 7] in dioxane/H_2O (5:1, 25:5 mL) was added K_2CO_3 (0.28 mg, 2.0 mmol), tetrakistriphenylphosphine Pd(0) (77 mg, 0.06 mmol), and trimethylboroxine (0.17 mL, 1.2 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 1:1) to give the title compound (0.10 g, 33%) as a white solid: LC-MS (ES) m/z = 455 $(M+H)^+$.

b) *N*-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl [2-({[4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (0.10 g, 0.22 mmol) was dissolved in MeOH (10 mL) and THF (5 mL) and treated with 4 M HCl in dioxane (5 mL). After 4 h, the solution was concentrated affording the HCl salt of the title compound (68 mg, 91%) as a white powder: LC-MS (ES) m/z = 355 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.79 (s, 1H), 7.68 (s, 1H), 7.31 (m, 4H), 7.25 (m, 1H), 6.56 (s, 1H), 4.54 (m, 1H), 3.87 (s, 3H), 3.69 (s, 2H), 3.34 (m, 2H), 3.03 (d, J = 7.6 Hz, 2H) and 2.21 (s, 3H).

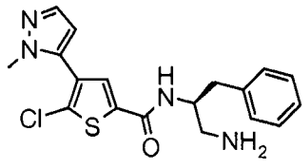
Example 17



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(3-furanyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

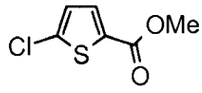
The title compound was prepared as a white solid according to the procedure of Example 16, except substituting 3-furan boronic acid (0.13 g, 1.2 mmole) for trimethylboroxine: LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 8.13 (s, 1H), 7.81 (s, 1H), 7.53 (m, 2H), 7.34 (m, 4H), 7.26 (m, 1H), 6.61 (s, 1H), 6.20 (s, 1H), 4.57 (m, 1H), 3.68 (s, 2H), 3.63 (s, 3H), 3.24 (m, 2H) and 3.07 (m, 2H)

Example 18



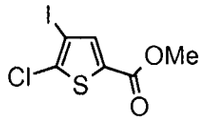
Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-2-thiophenecarboxylate



To a solution of 5-chloro-2-thiophenecarboxylic acid (2.0 g, 12.3 mmol) in dry MeOH (75 mL) was added H_2SO_4 (1 mL). The reaction mixture was heated to 50° C for 20h and was then concentrated under vacuum. The residue was dissolved in DCM and washed several times with saturated NaHCO3 solution. The organic fraction was dried (Na_2SO_4), concentrated under vacuum and used directly without further purification 21.3g, quant.): LC-MS (ES) m/z = 177 $(M+H)^+$.

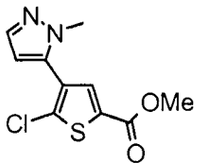
b) methyl 5-chloro-4-iodo-2-thiophenecarboxylate



To a solution of 5-chloro-2-thiophenecarboxylic acid (5.0 g, 28.0 mmol) in acetic acid (150 mL) was added $ZnCl_2$ (38g, 280 mmoles) and benzyltrimethylammonium dichloroiodate (20.5 g, 58.8 mmole) [*Bull. Chem. Soc.*

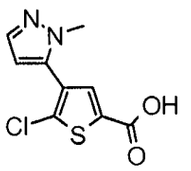
Jpn. **64**, 2566-2568 (1991)]. The reaction mixture was heated to 70° C for 48h and was then concentrated under vacuum. The residue was extracted with hexanes (2 x 200 mL) and the hexane solution washed with saturated $NaHCO_3$ solution. The organic fractions were dried (Na_2SO_4), concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 4:1) to give the title compound (3.8 g, 45%) as a light yellow solid: LC-MS (ES) m/z = 302 $(M+H)^+$.

c) methyl 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



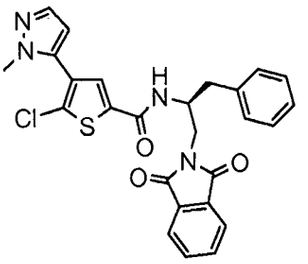
To a solution of methyl 5-chloro-4-iodo-2-thiophenecarboxylate (1.75 g, 5.8 mmol) in dioxane/H_2O (50:5 mL) was added K_2CO_3 (3.4 g, 24.9 mmol), tetrakistriphenylphosphine Pd(0) (0.96 g, 0.83 mmol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (3.4 g, 16.5 mmol). The reaction mixture was heated to 80° C in a sealed tube for 15h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 4:1) to give the title compound (0.35 g, 24%) as a yellow oil: LC-MS (ES) m/z = 257 $(M+H)^+$.

d) 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.30 g, 1.17 mmole) in THF (10 mL) and MeOH (10 mL) was added 6N NaOH (5 mL). The reaction solution was heated to 50°C for 2hrs. The reaction solution was concentrated under vacuum, made acidic (pH ~ 2) with 3N HCl, and extracted with DCM. The organic solution was dried (Na_2SO_4) and concentrated to a solid (0.22 g) which was used without further purification. LC-MS (ES) m/z = 243 $(M+H)^+$.

e) 5-chloro-*N*-[(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



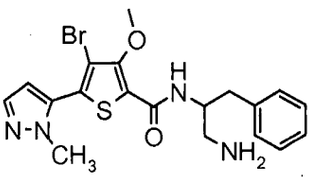
To a solution of 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (0.21 g, 0.87 mmol), PyBrOP (610 mg, 1.3mmol) and diisopropylethyl amine (0.76 mL, 4.35 mmol) in DCM (20 mL) at 25 °C was added 2-[(2*S*)-2-amino-3-phenylpropyl]-1*H*-isoindole-1,3(2*H*)-dione HCl (380 mg, 0.96 mmol)[prepared according to Preparation 5]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica) affording the title compound (200 mg, 46%) as a white solid: LC-MS (ES) m/z = 505 $(M+H)^+$.

f) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 5-chloro-*N*-[(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (200 mg, 0.40 mmol) in MeOH/THF (10 mL, 1:1) at RT was added hydrazine hydrate (0.20 mL, 4.0 mmol). After stirring for 24h at RT, the reaction solution was concentrated under vacuum and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound as a light yellow solid.

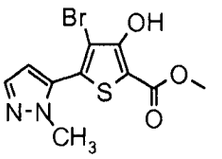
The neutral compound from above was dissolved in DCM (2 mL), treated with excess 4M HCl in dioxane (1mL) and concentrated affording the HCl salt (102 mg) of the title compound: LC-MS (ES) m/z = 375 $(M+H)^+$, 7.78 (s, 1H), 7.63 (s, 1H), 7.31 (m, 4H), 7.26 (m, 1H), 6.55 (s, 1H), 4.54 (m, 1H), 3.91 (s, 3H), 3.24 (m, 2H) and 3.03 (m, 2H).

Example 19



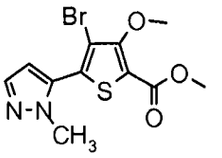
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-3-hydroxy-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



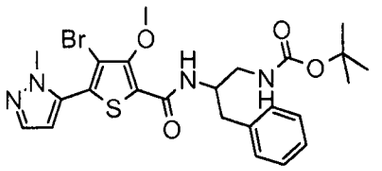
Methyl 4,5-dibromo-3-hydroxy-2-thiophenecarboxylate (500 mg, 1.59 mmol), 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (339 mg, 1.75 mmol), $Pd(PPh_3)_4$ (92 mg, 79.4 µmol) and K_2CO_3 (876 mg, 6.35 mmol) in dioxane (6.6 mL) and H_2O (1.3 mL) were combined in a sealed tube. After 12h at 80 °C, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 0.5 % MeOH in DCM) affording the title compound (75 mg, 15%) as a brown residue: LCMS (ES) m/z = 318 $(M+H)^+$.

b) methyl 4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-3-hydroxy-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (175 mg, 0.554 mmol), MeOH (26 µL, 0.609 mmol), PPh_3 (189 mg, 0.720 mmol) in THF (6 mL) at 25 °C was added DEAD (113 µL, 0.720 mmol) in one portion. After 30 min, the reaction was concentrated and purified via column chromatography (silica, 20% EtOAc in hexanes) affording the title compound (135 mg, 74%) as a white solid: LC-MS (ES) m/z = 332 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



i) A solution of methyl 4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (135 mg, 0.410 mmol) in 6N NaOH (4 mL) and THF (4 mL) was stirred in a sealed tube at 80 °C. After 2h, the solution was acidified to pH 3 using 1N HCl then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 318 $(M+H)^+$.

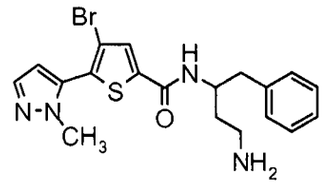
ii) To a solution of the crude acid, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (88 mg, 0.351 mmol)[from Preparation 2], diisopropylethyl amine (305 µL, 1.76 mmol) in DCM (3.5 mL) was added PyBrop (196 mg, 0.422 mmol) in one portion. After 12h, additional diisopropylethyl amine (305 µL, 1.76 mmol) and PyBrop (196 mg, 0.422 mmol) were added. After 2h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 550 $(M+H)^+$.

d) N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [2-({[4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part e) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (3% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

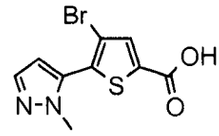
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound as the HCl salt: LC-MS (ES) m/z 450 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.07 (br. s., 3 H) 7.85 (d, J=8.84 Hz, 1 H) 7.58 (d, J=2.02 Hz, 1 H) 7.32 (d, J=7.07 Hz, 2 H) 7.26 - 7.29 (m, 2 H) 7.20 - 7.24 (m, 1 H) 6.54 (d, J=2.02 Hz, 1 H) 4.50-4.55 (m, 1H) 3.79 (d, J=6.82 Hz, 3 H) 3.74 (d, J=6.57 Hz, 1 H) 3.17 (s, 1 H) 2.98-3.10 (m, 4 H).

Example 20



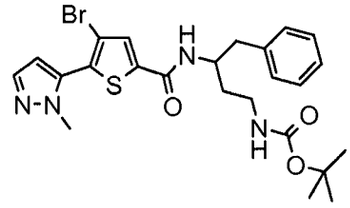
Preparation of *N*-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4,5-dibromo-2-thiophenecarboxylic acid (1 g, 3.5 mmol) in dioxane/H_2O (5:1, 18 mL) was added K_2CO_3 (1.9 g, 13.98 mmol), tetrakistriphenylphosphine Pd(0) (201 mg, 0.175 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (678 mg, 3.5 mmol). The reaction mixture was heated to 80° C in a sealed tube for 12h and was then partitioned between 6N NaOH and DCM. The pH of the aqueous phase was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (~1 g, quant.): LC-MS (ES) m/z = 288 $(M+H)^+$.

b) 1,1-dimethylethyl [3-({[4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-4-phenylbutyl]carbamate



To a solution of 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (250 mg, 0.874 mmol), PyBrOP (489 mg, 8.74 mmol) and diisopropylethyl amine (762 µL, 4.37 mmol) in DCM (8 mL) at 25 °C was added 1,1-dimethylethyl (3-

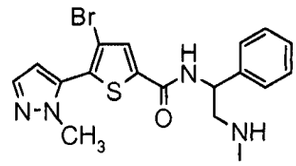
amino-4-phenylbutyl)carbamate (230 mg, 0.874 mmol)[prepared according to Preparation 8]. After 16h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica) affording the title compound (130 mg, 29%) as a white solid: LC-MS (ES) m/z = 533 $(M+H)^+$.

c) N-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [3-({[4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-4-phenylbutyl]carbamate (130 mg, 0.24 mmol) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (3% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (40 mg, 40%) as the HCl salt: LC-MS (ES) m/z 433 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.68 (d, J=8.59 Hz, 1 H) 7.97 (s, 1 H) 7.77 (br s, 3 H) 7.57 (d, J=2.02 Hz, 1 H) 7.28 (d, J=2.27 Hz, 3 H) 7.25 - 7.32 (m, 2 H) 6.55 (d, J=2.02 Hz, 1 H) 4.17 - 4.24 (m, 1 H) 3.78 (s, 3 H) 2.77 - 2.89 (m, 4 H) 1.85 - 1.92 (m, 1 H) 1.81 (td, J=9.54, 4.93 Hz, 1 H).

Example 21

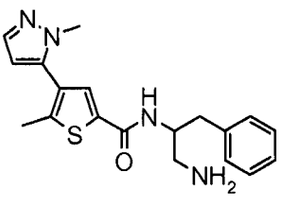


Preparation of 4-bromo-N-[2-(methylamino)-1-phenylethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 1, except substituting 1,1-dimethylethyl (2-amino-2-phenylethyl)methylcarbamate (1 g, 4.02 mmol) [Prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate and substituting 4,5-dibromo-2-thiophenecarboxylic acid (1.89 g, 6.6 mmol) for 4,5-

dibromo-2-furancarboxylic acid: LCMS (ES) m/z 420 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.64 (d, J=8.34 Hz, 1 H) 8.91 (br. s., 1 H) 8.33 (s, 1 H) 7.58 (d, J=2.02 Hz, 1 H) 7.42 - 7.50 (m, 2 H) 7.38 - 7.42 (m, 2 H) 7.34 (d, J=7.07 Hz, 1 H) 6.56 (d, J=2.02 Hz, 1 H) 5.37 - 5.44 (m, 1 H) 3.79 (s, 3 H) 3.47 - 3.54 (m, 1 H) 3.33 (td, J=8.46, 3.79 Hz, 1 H) 2.63 (t, J=5.31 Hz, 3 H).

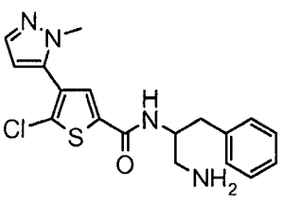
Example 22



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (81 mg, 0.368 mmol)[from Preparation 10] for 4,5-dibromo-2-furancarboxylic acid: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J=8.34 Hz, 1 H) 8.15 (br. s., 3 H) 8.00 (s, 1 H) 7.52 (d, J=1.77 Hz, 1 H) 7.24 - 7.31 (m, 4 H) 7.17 - 7.23 (m, 1 H) 6.36 (d, J=1.77 Hz, 1 H) 4.35 (d, J=3.03 Hz, 1 H) 3.78 (s, 3 H) 3.03 (dd, J=6.82, 2.53 Hz, 1 H) 2.93 - 2.99 (m, 2 H) 2.90 (d, J=6.06 Hz, 1 H) 2.38 (s, 3 H).

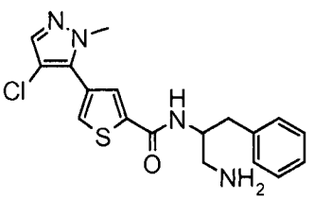
Example 23



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

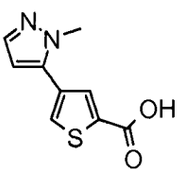
The title compound was prepared as a white solid according to the procedure of Example 1, except substituting 4-bromo-5-chloro-2-thiophenecarboxylic acid (250 mg, 1.04 mmol)[from Preparation 11] for 4,5-dibromo-2-furancarboxylic acid: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.09 (d, J=8.59 Hz, 1 H) 8.14 (s, 3 H) 8.10 (br. s., 1 H) 7.55 (d, J=1.77 Hz, 1 H) 7.25 - 7.32 (m, 4 H) 7.21 (dd, J=6.19, 2.40 Hz, 1 H) 6.48 (d, J=2.02 Hz, 1 H) 4.35 (d, J=8.59 Hz, 1 H) 3.84 (s, 3 H) 2.99 (d, J=10.86 Hz, 1 H) 2.89 - 2.96 (m, 3 H).

Example 24



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

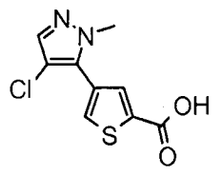
a) 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4-bromo-2-thiophenecarboxylic acid (1 g, 4.83 mmol) in dioxane/H_2O (5:1, 16 mL) was added K_2CO_3 (2.7 g, 19 mmol), tetrakistriphenylphosphine Pd(0) (279 mg, 0.241 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h and additional tetrakistriphenylphosphine Pd(0) (279 mg, 0.241 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol) were added. After 12h, the reaction was partitioned between 6N NaOH and DCM. The pH of the aqueous

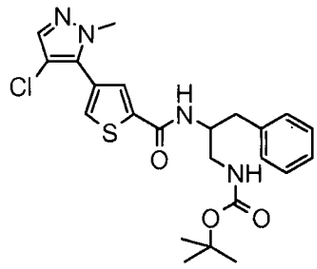
phase was adjusted to ~3 with 3M HCl and washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (~1 g, quant.): LCMS (ES) m/z = 209 $(M+H)^+$.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (600 mg, 2.88 mmol) and N-chlorosuccinimide (384 mg, 2.88 mmol) in THF (14 mL) was stirred in a sealed tube at 70 °C. After 1h, the solution was partitioned between H_2O-DCM, the aqueous phase was adjusted to pH 3 and the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (698 mg, quant.): LCMS (ES) m/z = 243 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (350 mg, 1.45 mmol), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (362 mg, 1.45 mmol)[from Preparation 2] and diisopropylethyl amine (1.3 mL, 7.23 mmol) in DCM (7 mL) was added PyBrop (809 mg, 1.74 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase

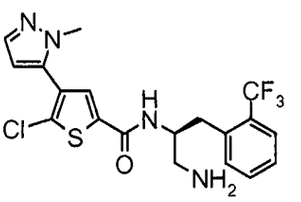
was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 476 $(M+H)^+$.

d) N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [2-({[4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part c) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30 min, the solution was concentrated and the residue neutralized through a silica plug (4% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

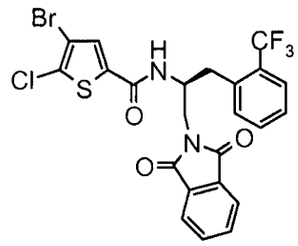
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (90 mg, 17%-2steps) as the HCl salt: LCMS (ES) m/z 476 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (d, J=8.08 Hz, 1 H) 8.10 (d, J=1.52 Hz, 2 H) 8.08 (s, 3 H) 7.68 (s, 1 H) 7.26 - 7.32 (m, 4 H) 7.22 (dd, J=6.06, 2.53 Hz, 1 H) 4.39 (br. s., 1 H) 3.87 (s, 3 H) 2.91 (d, J=7.33 Hz, 4 H).

Example 25



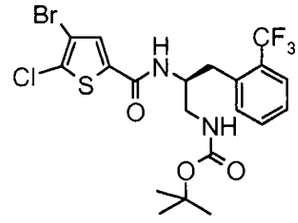
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



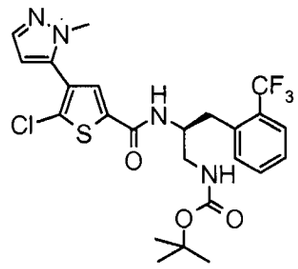
To a solution of 4-bromo-5-chloro-2-thiophenecarboxylic acid (1.3 g, 5.42 mmol), PyBrOP (3 g, 6.5 mmol) and diisopropylethyl amine (4.7 mL, 27.1 mmol) in DCM (54 mL) at 25 °C was added 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (2.0 g, 5.42 mmol)[prepared in Preparation 6]. After 1h, the solution was partitioned between H_2O and washed with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and used directly: LCMS (ES) m/z = 572 $(M+H)^+$.

b) 1,1-dimethylethyl {(2S)-2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



To a solution of 4-bromo-5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (crude from part a) in THF-MeOH (1:1, 20 mL) was added hydrazine (1.59 mL, 54.2 mmol). After 12h, the solution was filtered and the filtrate concentrated, dry loaded onto silica and purified via column chromatography (2% MeOH in DCM (1% NH_4OH)) affording the free base which was dissolved in THF (25 mL) and treated with Boc_2O (1.2 g, 5.31 mmol). After 30 min the solution was concentrated affording a white powder of the title compound (800 mg, 27%-3 steps): LCMS (ES) m/z = 542 $(M+H)^+$.

c) 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



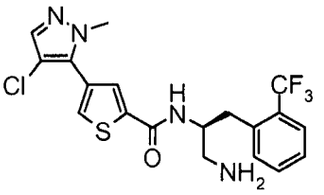
To a solution of 1,1-dimethylethyl {(2S)-2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (750 mg, 1.38 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (762 mg, 5.52 mmol), tetrakistriphenylphosphine Pd(0) (80 mg, 69 umol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (373 mg, 1.8 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h where additional tetrakistriphenylphosphine Pd(0) (80 mg, 69 umol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (373 mg, 1.8 mmol) were added. After 12h, the solution was poured onto H_2O (100 mL) and extracted with DCM. The organics were dried (Na_2SO_4), concentrated under vacuum, and purified on silica gel (hexanes/EtOAc, 1:1) to give the title compound (194 mg, 26%) as a white solid: LC-MS (ES) m/z = 544.

c) *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (194 mg, 0.357 mmol) was dissolved in TFA-DCM (3 mL, 1:2) and stirred at 25 °C. After 30min, the solution was concentrated with a toluene azeotrope and the residue neutralized through a silica plug (2-5% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

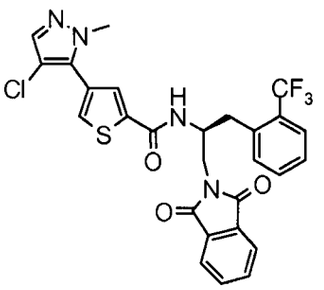
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (134 mg, 85%) as the HCl salt: LCMS (ES) m/z 444 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.10 (d, J=9.09 Hz, 1 H) 8.11 (s, 1 H) 8.10 (bs, 3 H) 7.70 (d, J=8.08 Hz, 1 H) 7.57 (d, J=2.02 Hz, 2 H) 7.43 (s, 1 H) 6.49 (d, J=2.02 Hz, 1 H) 4.47 (br. s., 1 H) 3.85 (s, 3 H) 3.06 (d, J=8.34 Hz, 4 H).

Example 26



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



The title compound was prepared as white solid according to the procedure of Example 24, except substituting 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (288 mg, 0.826 mmol)[from Preparation 6] for 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate: LCMS (ES) m/z 444 $(M+H)^+$.

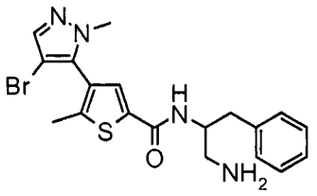
b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (150 mg, 0.262 mmol) in THF-MeOH (1:1, 2 mL) was added hydrazine (123 uL, 2.62 mmol). After 12h, the solution was filtered and the filtrate was concentrated, dry loaded onto silica and purified via column chromatography (2% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (30 mg, 26%) as the HCl salt: LCMS (ES) m/z 444 $(M+H)^+$, 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.69 (s, 1 H) 8.11 (d, *J*=1.26

Hz, 1 H) 8.03 (d, *J*=1.26 Hz, 1 H) 7.93 (bs, 3H) 7.69 (s, 2 H) 7.53 - 7.59 (m, 2 H) 7.44 (d, *J*=4.80 Hz, 1 H) 4.49 (br. s., 1 H) 3.87 (s, 3 H) 2.99 - 3.12 (m, 4 H).

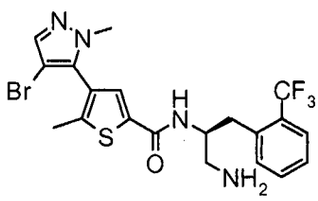
Example 27



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting NBS (325 mg, 2.43 mmol) for NCS: LCMS (ES) m/z 434 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (br. s., 1 H) 8.01 (br. s., 3 H) 7.80 (s, 1 H) 7.70 (s, 1 H) 7.25 - 7.32 (m, 4 H) 7.21 (td, J=6.19, 2.78 Hz, 1 H) 4.31 - 4.35 (m, 1 H) 3.71 (s, 3 H) 2.86 - 2.92 (m, 4 H) 2.33 (s, 3 H).

Example 28

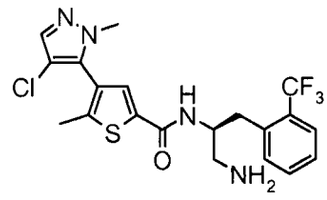


Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 26, except substituting 4-bromo-5-methyl-2-

thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting NBS (325 mg, 2.43 mmol) for NCS: LCMS (ES) m/z 502 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (br. s., 1 H) 8.05 (br. s., 3 H) 7.83 - 7.90 (m, 1 H) 7.67 - 7.74 (m, 2 H) 7.53 - 7.60 (m, 2 H) 7.39 - 7.47 (m, 1 H) 4.48 (d, J=5.05 Hz, 1 H) 3.68 - 3.76 (m, 3 H) 3.01 - 3.08 (m, 4 H) 2.33 (s, 3 H).

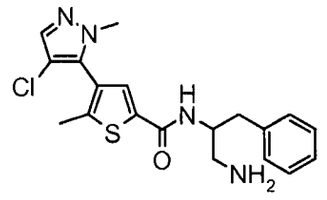
Example 29



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 26, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LCMS (ES) m/z 457 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (br. s., 1 H) 8.03 (br. s., 3 H) 7.86 (s, 1 H) 7.70 (s, 2 H) 7.53 - 7.60 (m, 2 H) 7.39 - 7.47 (m, 1 H) 4.46 (d, J=9.35 Hz, 1 H) 3.72 (s, 3 H) 3.03 - 3.10 (m, 4 H) 2.34 (s, 3 H).

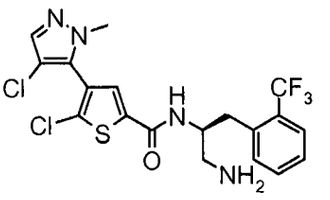
Example 30



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

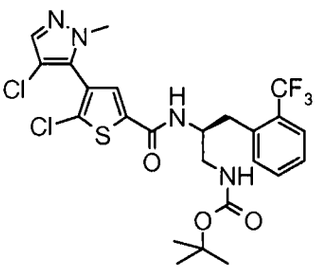
The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (1g, 4.52 mmol)[from Preparation 9] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LCMS (ES) m/z 389 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.67 (br. s., 1 H) 8.01 (br. s., 3 H) 7.82 (s, 1 H) 7.70 (s, 1 H) 7.25 - 7.32 (m, 4 H) 7.19 - 7.23 (m, 1 H) 4.31 - 4.38 (m, 1 H) 3.71 (s, 3 H) 2.97 (br. s., 2 H) 2.89 (t, J=6.19 Hz, 2 H) 2.34 (s, 3 H).

Example 31



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



A solution of 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (110 mg, 0.202 mmol)[prepared in Example 25] and N-chlorosuccinimide (35 mg, 0.263 mmol) in THF (2 mL) was stirred in a sealed tube at 70 °C. After 1h, the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4),

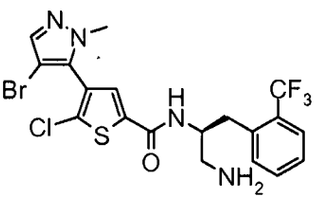
concentrated under vacuum and used directly without further purification: LCMS (ES) m/z = 578 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (crude from part a) was dissolved in TFA-DCM (3 mL, 1:2) and stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (5% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

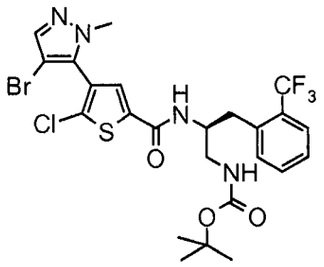
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (43 mg, 44%-2 steps) as the HCl salt: LCMS (ES) m/z 478 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.10 (d, J=8.84 Hz, 1 H) 8.06 (s, 4 H) 7.75 (s, 1 H) 7.70 (d, J=7.83 Hz, 1 H) 7.54 - 7.61 (m, 2 H) 7.43 (t, J=7.45 Hz, 1 H) 4.47 (t, J=8.84 Hz, 1 H) 3.78 (s, 3 H) 2.98 – 3.12 (m, 4 H).

Example 32



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 1,1-dimethylethyl {(2S)-2-({[4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate



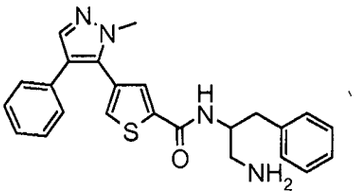
A solution of 1,1-dimethylethyl {(2S)-2-({[5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (121 mg, 0.22 mmol)[prepared in Example 25] and N-bromosuccinimide (52 mg, 0.290 mmol) in THF (2 mL) was stirred in a sealed tube at 70 °C. After 1h, the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification: LCMS (ES) m/z = 622 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

1,1-dimethylethyl {(2S)-2-({[4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-3-[2-(trifluoromethyl)phenyl]propyl}carbamate (crude from part a) was dissolved in TFA-DCM (3 mL, 1:2) and stirred at 25 °C. After 30 min, the solution was concentrated and the residue neutralized through a silica plug (5% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

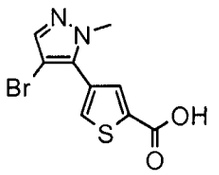
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (42 mg, 44%-2 steps) as the HCl salt: LCMS (ES) m/z 522 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.13 (d, J=9.09 Hz, 1 H) 8.17 (br. s., 1 H) 8.05 (s, 3 H) 7.75 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.54 - 7.61 (m, 2 H) 7.43 (t, J=7.58 Hz, 1 H) 4.46 (d, J=9.60 Hz, 1 H) 3.78 (s, 3 H) 2.99 – 3.13 (m, 4 H).

Example 33



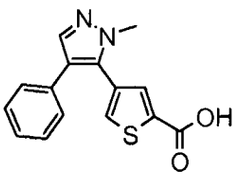
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



The title compound was prepare as an orange oil according to Example 24, except substituting N-bromosuccinimide (1 g, 5.77 mmol) for N-chlorosuccinimide: LCMS (ES) m/z 288 $(M+H)^+$.

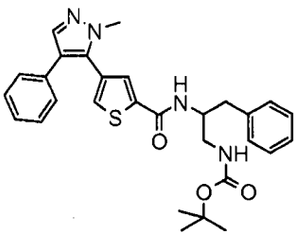
b) 4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (688 mg, 2.41 mmol) in dioxane/H_2O (5:1, 12 mL) was added K_2CO_3 (1.3 g, 9.6 mmol), tetrakistriphenylphosphine Pd(0) (139 mg, 0.120 mmol), and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (293 mg, 2.41 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h where additional tetrakistriphenylphosphine Pd(0) (139 mg, 0.120 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (293 mg, 2.41 mmol) were added. After 12h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title

compound white was used directly without further purification: LC-MS (ES) m/z = 284 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



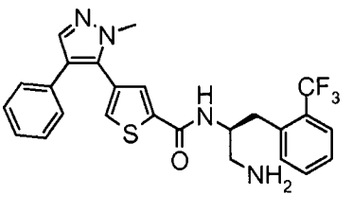
To a solution of 4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (341 mg, 1.2 mmol), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (300 mg, 1.2 mmol)[from Preparation 2], diisopropylethyl amine (1 mL, 6.01 mmol) in DCM (6 mL) was added PyBrop (673 mg, 1.44 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 517 $(M+H)^+$.

d) N-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [2-({[4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part c) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated and the residue neutralized through a silica plug (4% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

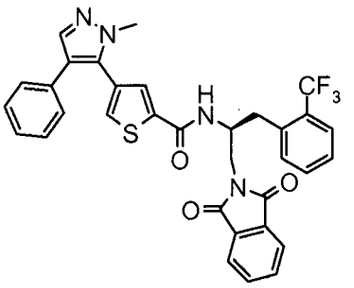
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (105 mg, 21%-3steps) as the HCl salt: LCMS (ES) m/z 417 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.82 (d, J=8.34 Hz, 1 H) 8.14 (br. s., 3 H) 7.96 (s, 1 H) 7.90 (d, J=1.26 Hz, 1 H) 7.82 (s, 1 H) 7.29 (s, 1 H) 7.25 (t, J=8.46 Hz, 9 H) 4.34 (dd, J=7.45, 5.68 Hz, 1 H) 3.75 (s, 3 H) 2.94 - 3.00 (m, 2 H) 2.89 (dd, J=6.82, 5.31 Hz, 2 H).

Example 34



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



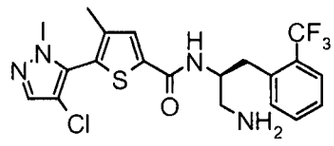
The title compound was prepared as a white solid according to the procedure of Example 33, except substituting 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (420 mg, 1.2 mmol) [from Preparation 6] for 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate: LCMS (ES) m/z 615 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (crude from part a) in THF-MeOH (1:1, 10 mL) was added hydrazine (384 uL, 12 mmol). After 12h, the solution was filtered and the filtrate was concentrated, dry loaded onto silica and purified via column chromatography (2% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

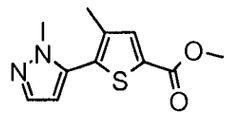
The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (40 mg, 7%) as the HCl salt: LCMS (ES) m/z 485 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (d, J=9.09 Hz, 1 H) 8.05 (br. s., 3 H) 7.91 (dd, J=9.09, 1.26 Hz, 2 H) 7.83 (s, 1 H) 7.69 (d, J=7.33 Hz, 1 H) 7.50 - 7.53 (m, 1 H) 7.43 (d, J=7.58 Hz, 1 H) 7.47 (t, J=6.82 Hz, 1 H) 7.23 - 7.30 (m, 4 H) 7.22 (s, 1 H) 4.47 (br. s., 1 H) 3.75 (s, 3 H) 3.01 (d, J=8.08 Hz, 4 H).

Example 35



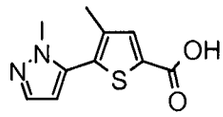
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

a) methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 5-bromo-4-methyl-2-thiophenecarboxylate (1 g, 4.25 mmol) in dioxane/H_2O (5:1, 20 mL) was added K_2CO_3 (2.3 g, 17 mmol), bis(tri-t-butylphosphine)palladium(0) (108 mg, 0.213 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 5.52 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h and additional tetrakistriphenylphosphine Pd(0) (279 mg, 0.241 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol) were added. After 12h, the reaction was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification: LCMS (ES) m/z = 237 $(M+H)^+$.

b) 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid

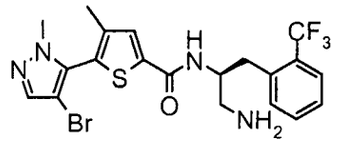


A solution of methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (crude from part a) in THF (4 mL) and 6N NaOH (4 mL) was heated to 70 °C. After 1h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title compound as a white solid which was used directly without further purification: LCMS (ES) m/z = 223 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

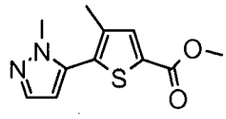
The title compound was prepared as a white solid according to the procedure of Example 27, except substituting 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (424 mg, 1.92 mmol) for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LCMS (ES) m/z 457 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J=8.84 Hz, 1 H) 8.05 (br. s., 3 H) 7.84 (s, 1 H) 7.74 (s, 1 H) 7.71 (d, J=8.08 Hz, 1 H) 7.56 - 7.63 (m, 2 H) 7.44 (t, J=7.20 Hz, 1 H) 4.47 - 4.54 (m, 1 H) 3.70 (s, 3 H) 2.93 - 3.12 (m, 4 H) 2.10 (s, 3 H).

Example 36



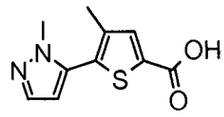
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

a) methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 5-bromo-4-methyl-2-thiophenecarboxylate (1 g, 4.25 mmol) in dioxane/H_2O (5:1, 20 mL) was added K_2CO_3 (2.3 g, 17 mmol), bis(tri-t-butylphosphine)palladium(0) (108 mg, 0.213 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 5.52 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h and additional tetrakistriphenylphosphine Pd(0) (279 mg, 0.24 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 6.27 mmol) were added. After 12h, the reaction was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification: LCMS (ES) m/z = 237 $(M+H)^+$.

b) 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



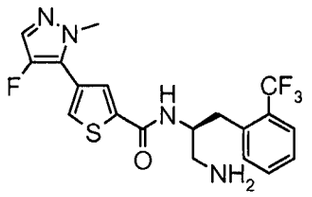
A solution of methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (crude from part a) in THF (4 mL) and 6N NaOH (4 mL) was heated to 70 °C. After 1h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title compound white was used directly without further purification: LCMS (ES) m/z = 223 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 26, except substituting 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (424 mg, 1.92 mmol) for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting N-bromosuccinimide (376 mg, 2.11 mmol) for N-chlorosuccinimide: LCMS (ES) m/z 502 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (d, J=9.09 Hz, 1 H) 8.05 (br. s., 3 H) 7.83 (s, 1 H) 7.67 - 7.74

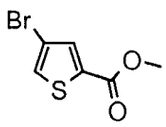
(m, 2 H) 7.60 (q, J=7.83 Hz, 2 H) 7.40 - 7.47 (m, 1 H) 4.50 (d, J=4.04 Hz, 1 H) 3.71 (s, 3 H) 2.98-3.12 (m, 4 H) 2.09 (s, 3 H).

Example 37



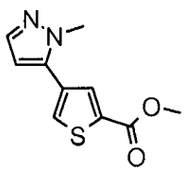
Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-2-thiophenecarboxylate



To a solution of 4-bromo-2-thiophenecarboxylic acid (4g, 19 mmol) in MeOH (100 mL) was added H_2SO_4 (5 mL) dropwise at 25 °C. The solution was stirred for 12 h at 50 °C and was poured into ice-H_2O and the pH was adjusted to ~11 with aqueous NaOH. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly (4.27g, quant.): LCMS (ES) m/z 222 $(M+H)^+$.

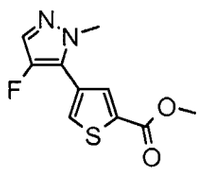
b) methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (1 g, 4.52 mmol) in dioxane/H_2O (5:1, 16 mL) was added K_2CO_3 (2.7 g, 19 mmol), bis(tri-t-butylphosphine)palladium(0) (116 mg, 0.226 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.2 g, 5.88 mmol). The reaction mixture was heated to 80° C in a sealed tube. After 1h, the reaction was partitioned

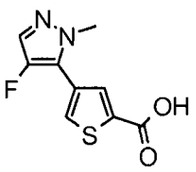
between H_2O-DCM and the aqueous phase was extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z 223 $(M+H)^+$.

c) methyl 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



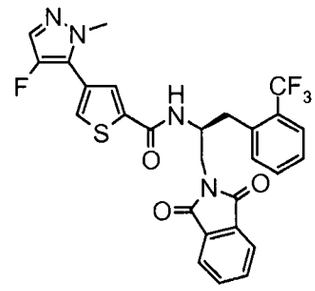
A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (330 mg, 1.49 mmol) and selectfluor ® (793 mg, 2.23 mmol) in THF (7 mL) and H_2O (500 uL) was stirred in a sealed tube at 70 °C. After 1h, additional selectfluor (793 mg, 2.23 mmol) was added and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM, the aqueous phase was washed several times with DCM. The combined organic fractions were dried (Na_2SO_4), concentrated and purified via column chromatography (silica, 20% EtOAc in hexanes) affording the title compound (126 mg, 33%) as a white solid: LCMS (ES) m/z = 241 $(M+H)^+$.

d) 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate
(126 mg, 0.53 mmol) in THF (1 mL) and 6N NaOH (1 mL) was heated to 70 °C. After 1h, the solution was poured onto H_2O and the pH was adjusted to ~4 with aqueous HCl. The aqueous phase was extracted several times with DCM and the combined organic fractions were dried (Na_2SO_4) and concentrated affording the title compound white was used directly without further purification: LCMS (ES) m/z = 227 $(M+H)^+$.

e) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



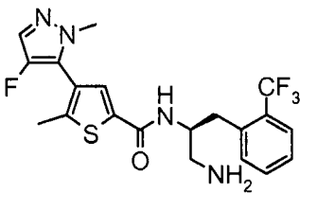
To a solution of 4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (84 mg, 0.372 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (130 mg, 0.372 mmol)[from Preparation 6], diisopropylethyl amine (323 uL, 1.86 mmol) in DCM (4 mL) was added PyBrop (208 mg, 0.446 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 0.5 % MeOH-DCM) affording the title compound (135 mg, 65%) as a white solid: LCMS (ES) m/z = 557 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (135 mg, 0.242 mmol) in THF-MeOH (1:1, 2 mL) was added hydrazine (75 uL, 2.42 mmol). After 12h, the solution was filtered and the filtrate was concentrated, dry loaded onto silica and purified via column chromatography (3% MeOH in DCM (1% NH_4OH)). The title compound was further purified via Gilson reverse phase chromatography using 5-95% mobile phase gradient affording the TFA-salt of the title compound which was neutralized through a silica plug ((5% MeOH in DCM (1% NH_4OH)) then transferred to the HCl salt using excess 4M HCl in dioxane (40 mg, 26%): LCMS (ES) m/z 427 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) d ppm 8.88 (d, J=8.84 Hz, 1 H) 8.13 (s, 1 H) 8.06 (bs, 3 H) 7.70 (d, J=7.83 Hz, 1

H) 7.55 - 7.62 (m, 3 H) 7.54 (br. s., 1 H) 7.41 (d, J=2.53 Hz, 1 H) 4.49 (d, J=5.05 Hz, 1 H) 3.92 (s, 3 H) 2.99 - 3.11 (m, 4 H).

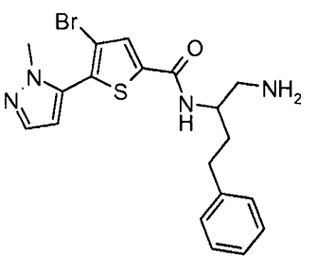
Example 38



Preparation of *N*-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 37, except substituting methyl 4-bromo-5-methyl-2-thiophenecarboxylate (1g, 4.26 mmol)[from Preparation 11] for methyl 4-bromo-2-thiophenecarboxylate: LCMS (ES) m/z 441 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d6) δ ppm 8.78 (d, J=9.60 Hz, 1 H) 8.03 (br s, 3 H) 7.91 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.62 (d, J=4.55 Hz, 1 H) 7.52 - 7.59 (m, 2 H) 7.39 - 7.46 (m, 1 H) 4.47 (br. s., 1 H) 3.74 (s, 3 H) 3.06 (br. s., 4 H) 2.36 (s, 3 H).

Example 39

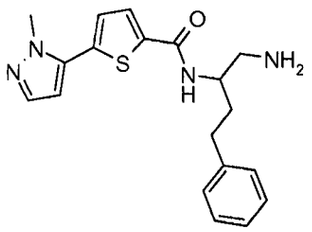


Preparation of *N*-[1-(aminomethyl)-3-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (2-amino-4-

phenylbutyl)carbamate (0.44 g, 1.7 mmol) [from Preparation 4] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z = 435 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.92 - 2.22 (m, 2 H) 2.71 - 2.82 (m, 2 H) 3.02 - 3.11 (m, 1 H) 3.12 - 3.24 (m, 1 H) 3.88 (s, 3 H) 4.30 (s, 1 H) 6.59 (d, *J*=1.77 Hz, 1 H) 7.17 (t, *J*=7.07 Hz, 1 H) 7.22 - 7.29 (m, 4 H) 7.67 (d, *J*=1.77 Hz, 1 H) 7.85 (s, 1 H).

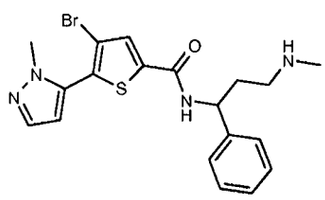
Example 40



Preparation of *N*-[1-(aminomethyl)-3-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (223 mg, 1.07 mmol) for 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate (0.51 g, 1.9 mmol) [from Preparation 4] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.87 - 1.99 (m, 2 H) 2.69 - 2.91 (m, 4 H) 4.00 - 4.07 (m, 3 H) 4.08 - 4.16 (m, 1 H) 6.56 (d, *J*=2.02 Hz, 1 H) 7.15 (t, *J*=6.95 Hz, 1 H) 7.20 - 7.28 (m, 4 H) 7.35 (d, *J*=3.79 Hz, 1 H) 7.51 (d, *J*=1.77 Hz, 1 H) 7.79 (d, *J*=3.79 Hz, 1 H).

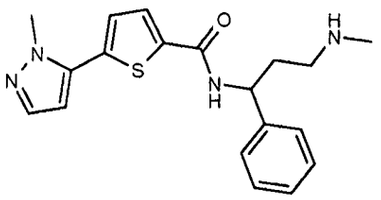
Example 41



Preparation of 4-bromo-*N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate (289 mg, 1.09 mmol) [from Preparation 12] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 435 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.12 - 2.23 (m, 2 H) 2.45 - 2.52 (m, 3 H) 2.64 - 2.74 (m, 1 H) 2.76 (dd, *J*=8.72, 5.94 Hz, 1 H) 3.77 - 3.88 (m, 3 H) 5.10 - 5.20 (m, 1 H) 6.52 (d, *J*=2.02 Hz, 1 H) 7.30 (d, *J*=6.82 Hz, 1 H) 7.35 - 7.45 (m, 4 H) 7.57 (d, *J*=1.77 Hz, 1 H) 7.89 (s, 1 H).

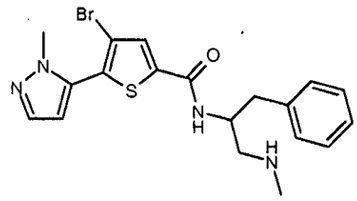
Example 42



Preparation of *N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (3-amino-3-phenylpropyl)methylcarbamate (430 mg, 1.63 mmol) [from Preparation 12] for 1,1-dimethylethyl (2-amino-4-phenylbutyl)carbamate and substituting 5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (224 mg, 1.08 mmol) for 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.18 - 2.28 (m, 2 H) 2.55 (s, 3 H) 2.77 - 2.85 (m, 1 H) 2.87 (dd, *J*=8.84, 5.81 Hz, 1 H) 4.01 (s, 3 H) 5.19 (dd, *J*=8.59, 6.57 Hz, 1 H) 6.55 (d, *J*=2.02 Hz, 1 H) 7.31 (d, *J*=7.07 Hz, 1 H) 7.34 - 7.41 (m, 3 H) 7.44 - 7.47 (m, 2 H) 7.50 (d, *J*=2.02 Hz, 1 H) 7.85 (d, *J*=4.04 Hz, 1 H).

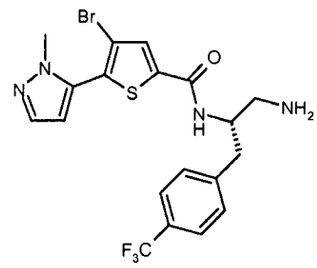
Example 43



Preparation of 4-bromo-*N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate (0.26 g, 1.09 mmol) [from Preparation 12] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 435 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.60 (s, 3 H) 2.90 - 3.01 (m, 2 H) 3.06 (d, *J*=6.57 Hz, 2 H) 3.83 (s, 3 H) 4.48 - 4.58 (m, 1 H) 6.52 (d, *J*=1.77 Hz, 1 H) 7.17 - 7.27 (m, 1 H) 7.27 - 7.33 (m, 4 H) 7.57 (d, *J*=2.02 Hz, 1 H) 7.77 (s, 1 H).

Example 44

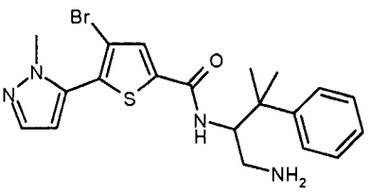


Preparation of *N*-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 6, except substituting 2-{(2*S*)-2-amino-3-[4-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (0.22 g, 0.62 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl. The reaction mixture was absorbed onto silica and purified via column chromatography to yield the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 489 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.04 - 3.30 (m, 4 H) 3.81 - 3.85 (m, 3 H) 4.59 (dd,

J=6.32, 3.28 Hz, 1 H) 6.52 (d, *J*=2.02 Hz, 1 H) 7.50 (d, *J*=8.08 Hz, 2 H) 7.58 (d, *J*=2.02 Hz, 1 H) 7.64 (d, *J*=8.08 Hz, 2 H) 7.73 (s, 1 H).

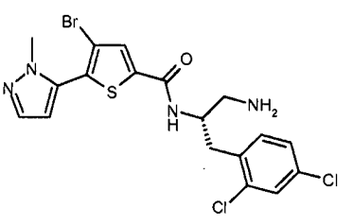
Example 45



Preparation of *N*-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (194 mg, 0.68mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2 -(2-amino-3-methyl-3-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione (0.20 g, 0.58 mmol) [prepared according to preparation 16] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 448 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.40 (s, 3 H) 1.47 (s, 3 H) 2.85 - 2.92 (m, 1 H) 3.01 (d, *J*=11.37 Hz, 1 H) 3.83 - 3.86 (m, 3 H) 4.74 (dd, *J*=11.37, 2.27 Hz, 1 H) 6.54 (d, *J*=2.02 Hz, 1 H) 7.28 (t, *J*=7.33 Hz, 1 H) 7.41 (t, *J*=7.71 Hz, 3 H) 7.52 (d, *J*=7.58 Hz, 2 H) 7.59 (d, *J*=2.02 Hz, 1 H) 7.89 (s, 1 H).

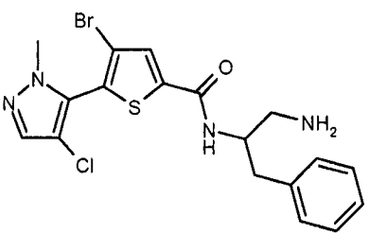
Example 46



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (135 mg, 0.47mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (153 mg, 0.44 mmol) [prepared according to the procedure of Preparation 6] for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 491 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.03 (dd, *J*=13.89, 9.35 Hz, 1 H) 3.14 - 3.21 (m, 1 H) 3.21 - 3.29 (m, 2 H) 3.84 (s, 3 H) 4.62 - 4.70 (m, 1 H) 6.53 (d, *J*=2.02 Hz, 1 H) 7.28 - 7.32 (m, 1 H) 7.33 - 7.37 (m, 1 H) 7.51 (d, *J*=2.02 Hz, 1 H) 7.58 (d, *J*=2.02 Hz, 1 H) 7.73 - 7.76 (m, 1 H).

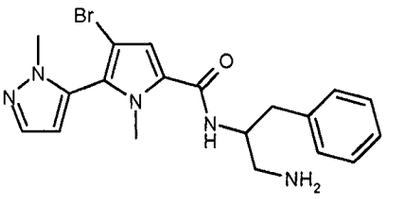
Example 47



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

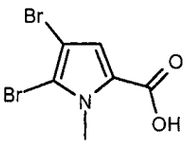
The title compound was prepared as a pale yellow solid according to the procedure of Example 30, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (2.84 g, 9.9mmol) for 4-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 457 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.95 - 3.07 (m, 4 H) 3.75 (s, 3 H) 4.44 (dd, *J*=6.44, 4.93 Hz, 1 H) 7.18 - 7.24 (m, 1 H) 7.27 - 7.32 (m, 4 H) 7.59 (s, 1 H) 7.86 (s, 1 H) .

Example 48



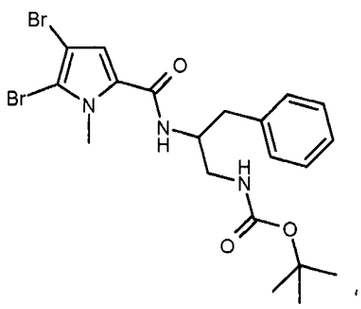
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

a) 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylic acid



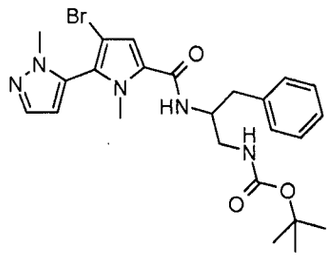
NBS (6.3 g, 35.4 mmol) was added in portions over 15 minutes to a stirred solution of 1-methyl-1*H*-pyrrole-2-carboxylic acid (2.1 g, 16.78 mmol) in DMF (30 mL) at 0 °C. Upon complete addition the mixture was slowly brought to 70°C. After 1h, the solution was partitioned between H_2O-$CHCl_3$, the aqueous phase was adjusted to pH 3 and the aqueous phase was washed several times with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4) and concentrated under vacuum to yield a 3:4 mixture of 5-bromo-1-methyl-1*H*-pyrrole-2-carboxylic acid and 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylic acid (3.4g) which was used directly without further purification: LCMS (ES) m/z = 206/286 $(M+H)^+$.

b) 1,1-dimethylethyl (2-{[(4,5-dibromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate



To a solution of 5-bromo-1-methyl-1*H*-pyrrole-2-carboxylic acid and 4,5-dibromo-1-methyl-1*H*-pyrrole-2-carboxylic acid (1.3 g), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (1.2 g, 4.8 mmol) [from Preparation 2] and PyBrop (2.6 g, 5.6 mmol) in $CHCl_3$ (30 mL) was added diisopropylethyl amine (2.8 mL, 16.1 mmol). The reaction mixture was stirred overnight, adsorbed onto silica and purified via column chromatography [1:3 EtOAc/hexanes] to give a 1:1 mixture of 1,1-dimethylethyl (2-{[(5-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate and 1,1-dimethylethyl (2-{[(4,5-dibromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate (800 mg): LCMS (ES) m/z = 438/518 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate



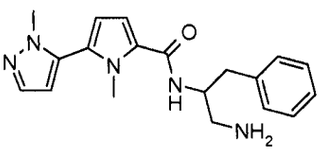
To a solution of a 1:1 mixture of 1,1-dimethylethyl (2-{[(5-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate and 1,1-dimethylethyl (2-{[(4,5-dibromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate (307 mg) in dioxane/H_2O (5:1, 5.6 mL) was added Cs_2CO_3 (800 mg, 2.5 mmol), tetrakistriphenylphosphine Pd(0) (44 mg, 0.04 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (157 mg, 0.75 mmol). The reaction mixture was heated to 80° C in a sealed tube for 2h after which additional tetrakistriphenylphosphine Pd(0) (20 mg, 0.02 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (177 mg, 0.85 mmol) were added. After 12h, the reaction mixture was adsorbed onto silica and purified via column chromatography to give two isomers: the title compound 1,1-dimethylethyl [2-({[4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (17 mg, 0.033 mmol) and 1,1-dimethylethyl [2-({[1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (20 mg, 0.05 mmol).

d) *N*-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

1,1-dimethylethyl [3-{[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]amino}-3-oxo-2-(phenylmethyl)propyl]carbamate (0.045 g, 0.09 mmol) dissolved in $CHCl_3$ (4 mL) and MeOH (1 mL) was treated with 4 M HCl in dioxane (2 mL). After stirring for 18h at RT, the reaction solution was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound as a white solid.

The neutral compound from above was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O (150 μL) and concentrated affording the HCl salt of the title compound: LC-MS (ES) m/z 418 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.76 - 2.98 (m, 4 H) 3.57 (d, *J*=2.78 Hz, 3 H) 3.71 (d, *J*=1.26 Hz, 3 H) 4.28 (ddd, *J*=8.27, 5.12, 2.78 Hz, 1 H) 6.44 (dd, *J*=7.58, 2.02 Hz, 1 H) 6.85 (s, 1 H) 7.18 - 7.24 (m, 1 H) 7.27 - 7.32 (m, 4 H) 7.61 (d, *J*=2.02 Hz, 1 H).

Example 49



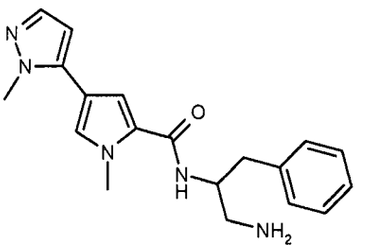
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

1,1-dimethylethyl [2-({[1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (20 mg, 0.05 mmol) [prepared in Example 48] in $CHCl_3$ (4 mL) and MeOH (1 mL) was treated with 4 M HCl in dioxane (2 mL). After stirring for 18h at RT, the reaction solution was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound.

The above compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O (150 μL) and concentrated affording the HCl salt of the title compound: LC-MS (ES) m/z 338 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.74 - 2.81 (m, 1 H) 2.83 - 2.90 (m, 2 H) 2.92 - 2.98 (m, 1 H) 3.63 (s, 3 H) 3.76 (s, 3 H)

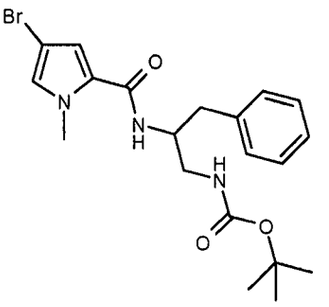
4.29 (ddd, *J*=8.02, 5.12, 2.53 Hz, 1 H) 6.27 (d, *J*=4.04 Hz, 1 H) 6.39 (d, *J*=2.02 Hz, 1 H) 6.80 (d, *J*=4.04 Hz, 1 H) 7.20 (td, *J*=5.87, 2.65 Hz, 1 H) 7.26 - 7.31 (m, 4 H) 7.57 (d, *J*=2.02 Hz, 1 H) .

Example 50



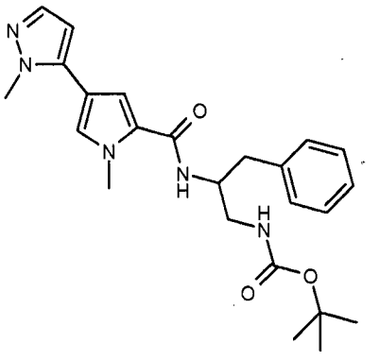
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

a) 1,1-dimethylethyl (2-{[(4-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate



To a 50 mL round-bottomed flask was added 4-bromo-1-methyl-1*H*-pyrrole-2-carboxylic acid (610 mg, 3.0 mmol), 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (748 mg, 2.99 mmol) [prepared according to the procedure of Preparation 2] and PyBrop (1.71 g, 3.67 mmol) in Chloroform (15 mL). DIEA (1.8 mL, 10.3 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (Hex/EtOAc) affording the title compound (335 mg, 26%): LC-MS (ES) m/z = 438 $(M+H)^+$.

b) 1,1-dimethylethyl [2-({[1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate

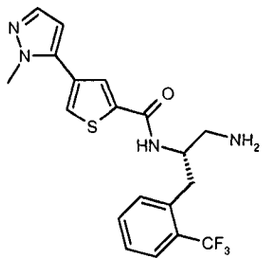


To a solution of 1,1-dimethylethyl (2-{[(4-bromo-1-methyl-1*H*-pyrrol-2-yl)carbonyl]amino}-3-phenylpropyl)carbamate (313 mg, 0.717 mmol) in dioxane/H_2O (4:1, 6.25 mL) was added Cs_2CO_3 (840 mg, 2.6 mmol), tetrakistriphenylphosphine Pd(0) (62 mg, 0.05 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (202 mg, 1.04 mmol). The reaction mixture was heated to 80 °C in a sealed tube for 12h and was then partitioned between H_2O and $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum, adsorbed onto silica gel and purified via column chromatography (35% EtOAc/Hex) affording the title compound (285 mg, 91%): LC-MS (ES) m/z = 438 $(M+H)^+$.

c) *N*-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide

HCl in Dioxane (4M, 2mL) was added to a solution of 1,1-dimethylethyl [2-({[1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrol-2-yl]carbonyl}amino)-3-phenylpropyl]carbamate (285 mg, 0.65 mmol) in CHCl3/MeOH (10:1, 10 mL) affording the title compound as a white solid (71 mg, 0.21 mmol, 32%): LC-MS (ES) m/z 338 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.77 - 2.93 (m, 4 H) 3.86 (s, 3 H) 3.92 (s, 3 H) 4.29 (ddd, *J*=8.15, 4.74, 2.02 Hz, 1 H) 6.30 (d, *J*=2.02 Hz, 1 H) 6.94 (d, *J*=1.77 Hz, 1 H) 7.14 (d, *J*=1.77 Hz, 1 H) 7.19 (td, *J*=5.56, 3.03 Hz, 1 H) 7.25 - 7.30 (m, 4 H) 7.41 (d, *J*=1.77 Hz, 1 H).

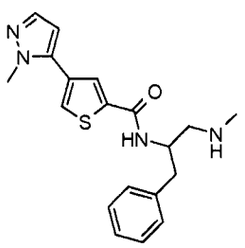
Example 51



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (232 mg, 1.11mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.09 - 3.30 (m, 4 H) 3.97 - 4.00 (m, 3 H) 4.62 - 4.72 (m, 1 H) 6.48 (d, *J*=2.02 Hz, 1 H) 7.43 (ddd, *J*=8.08, 4.42, 4.17 Hz, 1 H) 7.51 - 7.56 (m, 3 H) 7.72 (d, *J*=7.83 Hz, 1 H) 7.89 - 7.93 (m, 2 H).

Example 52

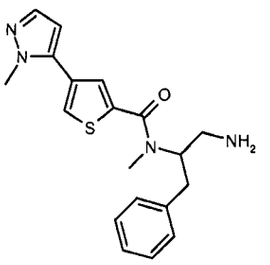


Preparation of *N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)methylcarbamate (0.32 g, 1.2 mmol) [from Preparation 13] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate and substituting 4-(1-methyl-1*H*-

pyrazol-5-yl)-2-thiophenecarboxylic acid (220 mg, 1.06 mmol) for 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.41 (s, 3 H) 2.81 (td, *J*=11.81, 7.96 Hz, 2 H) 2.87 - 2.97 (m, 2 H) 3.96 (s, 3 H) 4.43 - 4.52 (m, 1 H) 6.45 (d, *J*=1.52 Hz, 1 H) 7.16 - 7.23 (m, 1 H) 7.25 - 7.30 (m, 4 H) 7.50 (d, *J*=1.52 Hz, 1 H) 7.85 (d, *J*=13.14 Hz, 2 H).

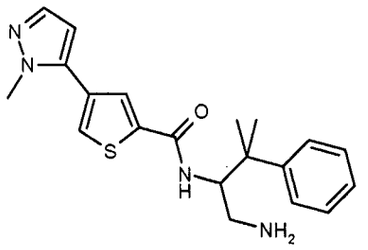
Example 53



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-*N*-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 2-[2-(methylamino)-3-phenylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.7 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl and substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (150 mg, 0.72 mmol) for 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.86 (s, 3 H) 2.97 (dd, *J*=14.02, 8.72 Hz, 2 H) 3.12 - 3.23 (m, 2 H) 3.70 (m, 1 H) 3.97 (s, 3 H) 6.47 (d, *J*=2.02 Hz, 1 H) 7.30 - 7.35 (m, 1 H) 7.37 - 7.43 (m, 5 H) 7.51 (d, *J*=2.02 Hz, 1 H) 7.88 (d, *J*=1.52 Hz, 1 H) 7.94 (d, *J*=1.52 Hz, 1 H).

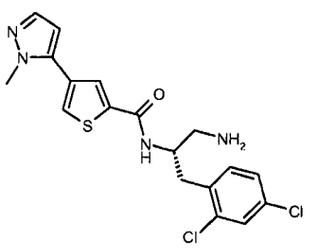
Example 54



Preparation of *N*-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (129 mg, 0.62 mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2 -(2-amino-3-methyl-3-phenylbutyl)-1*H*-isoindole-1,3(2*H*)-dione (0.20 g, 0.58 mmol) [prepared according to the procedure of Preparation 14] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 369 $(M+H)^+$, ^{1}H NMR (400 MHz, MeOD) δ ppm 1.36 (s, 3 H) 1.41 (s, 3 H) 2.61 (d, *J*=6.82 Hz, 2 H) 3.99 (s, 3 H) 4.49 (t, *J*=6.95 Hz, 1 H) 6.49 (d, *J*=1.77 Hz, 1 H) 7.23 (t, *J*=7.33 Hz, 1 H) 7.36 (t, *J*=7.71 Hz, 2 H) 7.47 - 7.52 (m, 3 H) 7.89 (d, *J*=1.26 Hz, 1 H) 8.00 (d, *J*=1.52 Hz, 1 H)).

Example 55

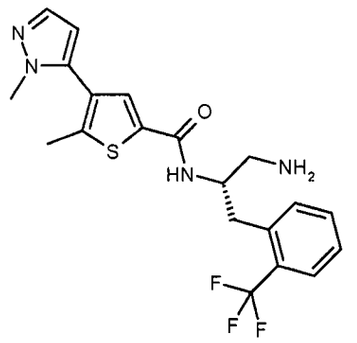


Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (99 mg, 0.48mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (155 mg, 0.44 mmol) [prepared

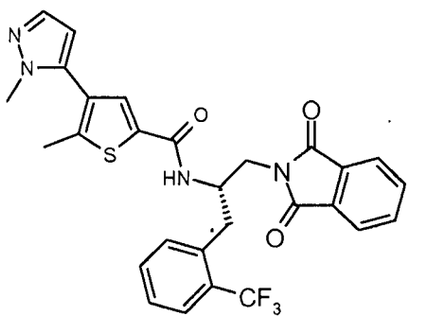
according to procedure of Preparation 6] for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine. The reaction mixture was absorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 411 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.05 - 3.28 (m, 4 H) 3.97 (s, 3 H) 4.63 - 4.72 (m, 1 H) 6.47 (d, *J*=2.02 Hz, 1 H) 7.26 - 7.29 (m, 1 H) 7.34 - 7.37 (m, 1 H) 7.49 (d, *J*=2.27 Hz, 1 H) 7.51 (d, *J*=2.02 Hz, 1 H) 7.86 (d, *J*=1.52 Hz, 1 H) 7.90 (d, *J*=1.52 Hz, 1 H).

Example 56



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (206 mg, 0.93 mmol) [prepared according

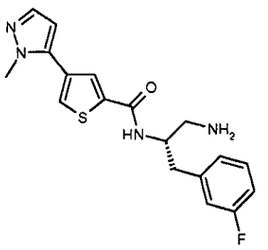
to the procedure of Preparation 9], 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (209 mg, 0.60 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (340 mg, 0.73 mmol) in Chloroform (15 mL). DIEA (0.81 mL, 4.65 mmol) was added and the mixture stirred overnight at room temperature. Upon completion, the reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (112 mg, 0.203 mmol, 22%): LC-MS (ES) m/z = 553 $(M+H)^+$

b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (112 mg, 0.203 mmol) in Tetrahydrofuran (THF) (6 mL) and Methanol (1 mL). Hydrazine (40 µL, 1.3 mmol) was added and the mixture stirred overnight at room temperature. Upon completion, the mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (43 mg, 0.102 mmol, 50 % yield): LC-MS (ES) m/z 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 3.01 (m, 1 H) 3.08 (d, *J*=6.57 Hz, 3 H) 3.76 - 3.83 (m, 3 H) 4.47 (m, 1 H) 6.37 (d, *J*=2.02 Hz, 1 H) 7.41 (t, *J*=7.58 Hz, 1 H) 7.50 - 7.57 (m, 2 H) 7.57 - 7.63 (m, 1 H) 7.68 (d, *J*=7.58 Hz, 1 H) 8.04 (d, *J*=9.09 Hz, 1 H) 8.15 (s, 3 H) 8.96 (s, 1 H).

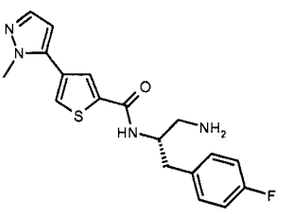
Example 57



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (222 mg, 1.07mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (357 mg, 1.2 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 359 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.96 - 3.06 (m, 4 H) 3.92 - 3.98 (m, 3 H) 4.40 (dd, *J*=8.08, 5.56 Hz, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.02 (td, *J*=8.46, 2.02 Hz, 1 H) 7.14 (t, *J*=8.08 Hz, 2 H) 7.26 - 7.35 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.16 - 8.27 (m, 3 H) 8.34 (d, *J*=1.26 Hz, 1 H) 9.08 (d, *J*=8.34 Hz, 1 H).

Example 58

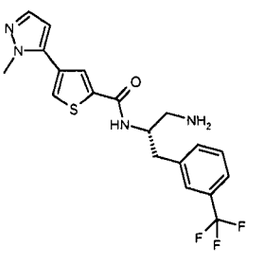


Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (138 mg, 0.66 mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (196 mg, 0.66 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-

1H-isoindole-1,3(2H)-dione-HCl. The reaction mixture was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 - 3.03 (m, 4 H) 3.89 - 3.97 (m, 3 H) 4.30 - 4.40 (m, 1 H) 6.45 (d, *J*=1.77 Hz, 1 H) 7.12 (t, *J*=8.84 Hz, 2 H) 7.29 (dd, *J*=8.34, 5.56 Hz, 2 H) 7.48 (d, *J*=1.77 Hz, 1 H) 7.92 (br. s, 3 H) 7.96 (d, *J*=1.26 Hz, 1 H) 8.02 (d, *J*=1.26 Hz, 1 H) 8.58 (d, *J*=8.84 Hz, 1 H).

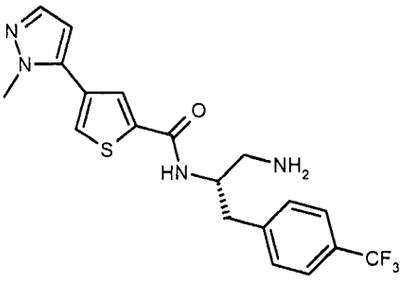
Example 59



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (189 mg, 0.91mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (297 mg, 0.85 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.06 (d, *J*=7.07 Hz, 4 H) 3.91 - 3.98 (m, 3 H) 4.35 - 4.45 (m, 1 H) 6.46 (d, *J*=1.77 Hz, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.49 - 7.57 (m, 2 H) 7.58 - 7.63 (m, 1 H) 7.69 (s, 1 H) 7.98 (d, *J*=1.52 Hz, 1 H) 8.23 (s, 3 H) 8.32 (d, *J*=1.26 Hz, 1 H) 9.11 (d, *J*=8.84 Hz, 1 H).

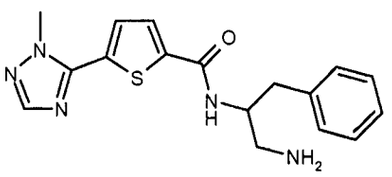
Example 60



Preparation of *N*-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

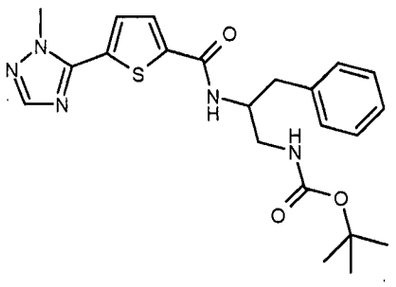
The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (240 mg, 0.9 mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substitiuting 2-{(2*S*)-2-amino-3-[4-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (278 mg, 0.80 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z 409 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.04 (m, 4 H) 3.96 (s, 3 H) 4.42 (s, 1 H) 6.44 - 6.49 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.52 (d, *J*=7.83 Hz, 2 H) 7.66 (d, *J*=8.08 Hz, 2 H) 8.01 (s, 1 H) 8.05 – 8.32 (br. m, 3H) 8.34 (m, 1H) 8.9 – 9.2 (br. s, 1 H).

Example 61



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

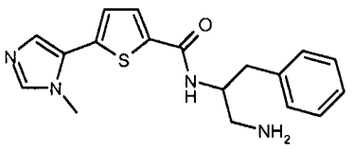


To a solution of 1,1-dimethylethyl [3-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)propyl]carbamate (154 mg, 0.32 mmol) [prepared according to the procedure of Example 3] in Dioxane / H_2O (5:1, 3.1 mL) was added Cs_2CO_3 (415 mg, 1.27 mmol), tetrakistriphenylphosphine Pd(0) (29 mg, 0.03 mmol), and 5-iodo-1-methyl-1*H*-1,2,4-triazole (95 mg, 0.46 mmol) [prepared according to the procedure of Preparation 15]. The reaction mixture was heated to 85 °C in a sealed tube for 12 hours. The reaction was partitioned between H_2O and $CHCl_3$, the organic layer dried with Na_2SO_4, absorbed onto silica and purified via column chromatography (35-50% EtOAc/Hexanes) affording the title compound as a yellow solid (61 mg, 28%): LC-MS (ES) m/z = 521.

b) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

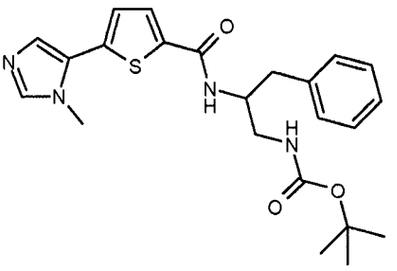
HCl in Dioxane (4M, 1mL) was added to a solution of 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (61 mg, 0.12 mmol) in $CHCl_3$/MeOH (10:1, 10 mL) and the mixture stirred overnight. Upon completion, the mixture was adsorbed onto silica gel and purified via chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound as a white solid (30 mg, 0.09 mmol, 77%): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.79 - 2.91 (m, 3 H) 2.94 (t, *J*=5.56 Hz, 1 H) 4.10 (s, 3 H) 4.25 - 4.34 (m, 1 H) 7.18 (ddd, *J*=8.27, 5.75, 3.16 Hz, 1 H) 7.24 - 7.29 (m, 4 H) 7.63 (d, *J*=4.04 Hz, 1 H) 7.75 (d, *J*=4.04 Hz, 1 H) 7.95 (s, 1 H).

Example 62



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-imidazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



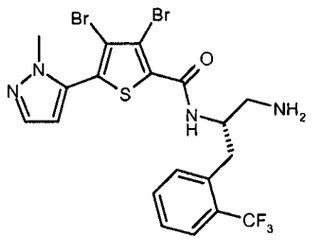
To a solution of 1,1-dimethylethyl [2-phenyl-2-({[5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-thienyl]carbonyl}amino)ethyl]carbamate (72 mg, 0.15 mmol) [prepared according to the procedure of Example 3] in dioxane/H_2O (5:1, 1.4 mL) was added Cs_2CO_3 (200 mg, 0.61 mmol), tetrakistriphenylphosphine Pd(0) (8.5 mg, 0.01 mmol), and 5-bromo-1-methyl-1*H*-imidazole (64 mg, 0.40 mmol). The reaction mixture was heated to 85 °C in a sealed tube for 12h. Upon completion, the reaction mixture was partitioned between H_2O (25 mL) and $CHCl_3$. The organics were dried (Na_2SO_4), concentrated under vacuum, adsorbed onto silica gel and purified via column chromatography (35 – 50% EtOAc / Hexanes) to give the title compound (19.6 mg, 31%) as a yellow solid: LC-MS (ES) m/z = 441.

b) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide

HCl in Dioxane (4M, 1mL) was added to a solution of 1,1-dimethylethyl [2-({[5-(1-methyl-1*H*-imidazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (19.6 mg, 0.04 mmol) in $CHCl_3$/MeOH (10:1, 5 mL). Upon completion of the reaction, the mixture was adsorbed onto silica gel and purified via chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound as a white solid (19 mg, 0.05 mmol, quant.): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.77 - 2.83 (m, 1 H) 2.85 - 2.91 (m, 2 H) 2.93 - 2.99 (m, 1 H) 3.82 (s, 3 H) 4.30 (ddd, *J*=8.08, 4.80, 1.77 Hz, 1 H) 7.15 - 7.31 (m, 7 H) 7.69 (d, *J*=4.04 Hz, 1 H) 7.76 (s, 1 H).

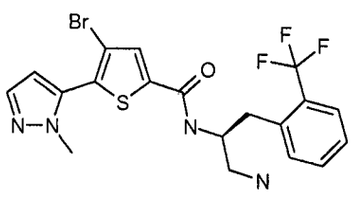
Example 63



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (253 mg, 0.69mmol) for 5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid. The reaction mixture was adsorbed onto silica and purified via column chromatography (silica, 3% MeOH in DCM (1% NH_4OH)) yielding the title compound, which was further purified by Gilson reverse phase chromatography 5-95% H_2O (1%TFA)/MeCN(1%TFA) to afford the TFA salt: LC-MS (ES) m/z 569 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.14 - 3.30 (m, 4 H) 3.82 (s, 3 H) 4.73 (dd, *J*=9.47, 4.67 Hz, 1 H) 6.54 (d, *J*=2.02 Hz, 1 H) 7.44 - 7.50 (m, 1 H) 7.56 - 7.62 (m, 3 H) 7.74 (d, *J*=7.83 Hz, 1 H).

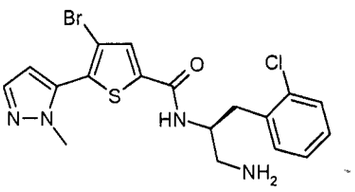
Example 64



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.50 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 488 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.15 (s, 2 H) 3.23 (s, 2 H) 3.84 (s, 3 H) 4.65 (s, 1 H) 6.52 - 6.57 (m, 1 H) 7.46 (s, 1 H) 7.52 - 7.61 (m, 3 H) 7.72 (s, 1 H) 7.81 (s, 1 H).

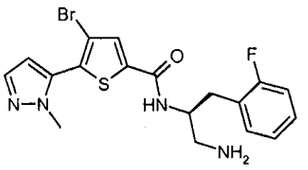
Example 65



Preparation of *N*-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (157 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 455 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.11 (s, 1 H) 3.22 (s, 1 H) 3.27 (s, 2 H) 3.85 (s, 3 H) 4.70 (s, 1 H) 6.57 (s, 1 H) 7.26 (s, 2 H) 7.41 (s, 2 H) 7.66 (s, 1 H) 7.88 (s, 1 H).

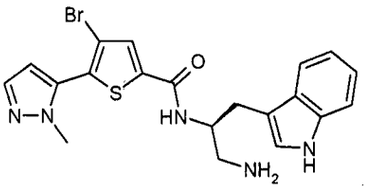
Example 66



Preparation of *N*-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (149 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 438 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.00 (s, 1 H) 3.09 (s, 1 H) 3.15 (dd, J=3.41, 1.64 Hz, 2 H) 3.83 (s, 4 H) 4.58 (s, 1 H) 6.52 (d, J=2.02 Hz, 1 H) 7.08 - 7.17 (m, 3 H) 7.27 - 7.37 (m, 3 H) 7.59 (d, J=2.02 Hz, 1 H) 7.74 (d, J=3.54 Hz, 1 H).

Example 67

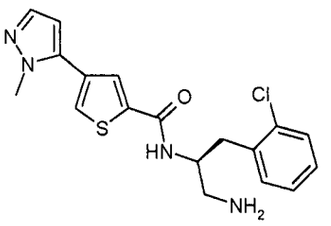


Preparation of *N*-[(1*S*)-2-amino-1-(1*H*-indol-3-ylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-thiophenecarboxylic acid (143 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(1*H*-indol-3-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-dione-HCl (160 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 459 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.15 (dt, J=10.42, 6.79 Hz,

3 H) 3.27 (dd, J=4.04, 2.27 Hz, 1 H) 3.84 (s, 3 H) 4.63 (d, J=6.82 Hz, 1 H) 6.54 (d, J=2.02 Hz, 1 H) 7.05 (t, J=7.45 Hz, 1 H) 7.13 (t, J=7.07 Hz, 1 H) 7.19 (s, 1 H) 7.37 (d, J=8.08 Hz, 1 H) 7.64 - 7.73 (m, 2 H) 7.77 (s, 1 H).

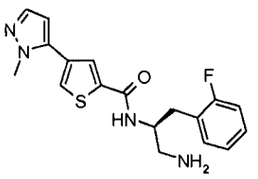
Example 68



Preparation of *N*-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (157 mg, 0.5 mmol) [prepared according to Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.11 - 3.20 (m, 1 H) 3.22 - 3.31 (m, 3 H) 4.23 (s, 3 H) 4.75 (s, 1 H) 6.96 (s, 1 H) 7.18 - 7.26 (m, 2 H) 7.38 (d, J=6.06 Hz, 1 H) 7.46 (d, J=4.55 Hz, 1 H) 8.22 (s, 2 H) 8.32 (s, 1 H).

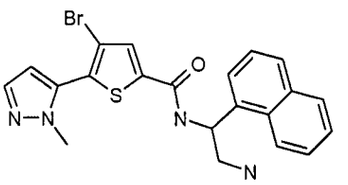
Example 69



Preparation of *N*-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(2-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (149 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.06 - 3.17 (m, 2 H) 3.25 - 3.31 (m, 2 H) 4.18 (s, 3 H) 4.59 - 4.67 (m, 1 H) 6.88 (s, 1 H) 7.05 - 7.12 (m, 2 H) 7.23 - 7.30 (m, 1 H) 7.36 - 7.42 (m, 1 H) 8.12 (d, J=1.01 Hz, 1 H) 8.17 (s, 1 H) 8.21 (s, 1 H).

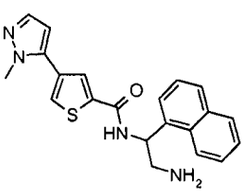
Example 70



Preparation of *N*-[2-amino-1-(1-naphthalenyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate (143 mg, 0.5 mmol) [from Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 456 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.60 (s, 1 H) 3.72 (s, 1 H) 3.84 (s, 3 H) 6.33 (d, J=10.11 Hz, 1 H) 6.55 (s, 1 H) 7.55 - 7.61 (m, 3 H) 7.64 (d, J=8.34 Hz, 1 H) 7.74 (s, 1 H) 7.92 - 7.99 (m, 2 H) 8.09 (s, 1 H) 8.26 (s, 1 H).

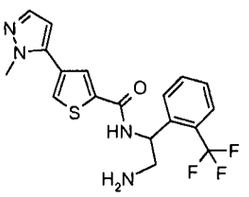
Example 71



Preparation of *N*-[2-amino-1-(1-naphthalenyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl [2-amino-2-(1-naphthalenyl)ethyl]carbamate (143 mg, 0.5 mmol) [from Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 377 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.62 (d, J=4.04 Hz, 1 H) 3.67 - 3.78 (m, 1 H) 4.08 - 4.10 (m, 3 H) 6.35 (s, 1 H) 6.73 (d, J=2.27 Hz, 1 H) 7.55 - 7.60 (m, 2 H) 7.62 - 7.67 (m, 1 H) 7.76 (d, J=7.33 Hz, 1 H) 7.88 (d, J=2.53 Hz, 1 H) 7.93 - 7.99 (m, 2 H) 8.10 (d, J=1.52 Hz, 1 H) 8.23 - 8.27 (m, 2 H).

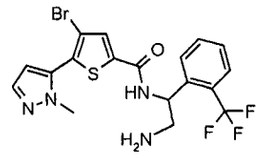
Example 72



Preparation of *N*-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl {2-amino-2-[2-(trifluoromethyl)phenyl]ethyl}carbamate (152 mg, 0.5 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.36 - 3.39 (m, 1 H) 3.46 - 3.53 (m, 1 H) 3.98 (s, 3 H) 5.86 - 5.91 (m, 1 H) 6.48 (s, 1 H) 7.51 (d, J=2.02 Hz, 1 H) 7.60 (s, 1 H) 7.76 (s, 1 H) 7.83 (d, J=8.08 Hz, 2 H) 7.94 (s, 1 H) 8.05 (s, 1 H).

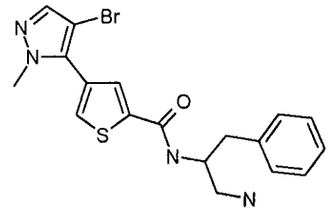
Example 73



Preparation of *N*-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl {2-amino-2-[2-(trifluoromethyl)phenyl]ethyl}carbamate (152 mg, 0.5 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 474 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.37 (s, 1 H) 3.65 (s, 1 H) 3.89 - 4.00 (m, 3 H) 5.88 (s, 1 H) 6.76 (d, J=2.27 Hz, 1 H) 7.58 (s, 1 H) 7.77 (d, J=9.60 Hz, 2 H) 7.91 - 8.03 (m, 2 H) 8.26 (d, J=2.27 Hz, 1 H).

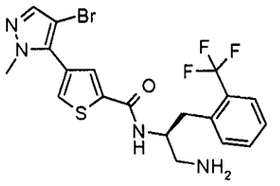
Example 74



Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 24, except substituting NBS (194 mg, 1.09 mmol) for NCS: LC-MS (ES) m/z 418 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.03 (d, J=7.33 Hz, 2 H) 3.23 (s, 2 H) 3.90 (s, 3 H) 4.56 (d, J=1.77 Hz, 1 H) 7.20 - 7.27 (m, 1 H) 7.28 - 7.34 (m, 4 H) 7.58 (s, 1 H) 7.96 (s, 2 H).

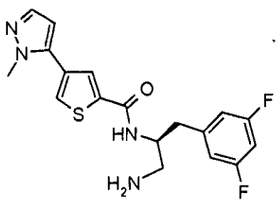
Example 75



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 25, except substituting NBS (67 mg, 0.5 mmol) for NCS: LC-MS (ES) m/z 488 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.10 - 3.19 (m, 1 H) 3.20 - 3.28 (m, 3 H) 3.91 (s, 3 H) 4.66 (dd, J=8.59, 3.03 Hz, 1 H) 7.39 - 7.47 (m, 1 H) 7.51 - 7.58 (m, 2 H) 7.59 (s, 1 H) 7.72 (d, J=8.08 Hz, 1 H) 7.98 (s, 2 H).

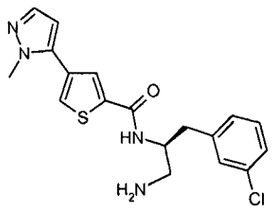
Example 76



Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione-HCl (158 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.94 - 3.06 (m, 4 H) 3.95 (s, 3 H) 4.40 (d, J=6.06 Hz, 1 H) 6.46 (d, J=1.77 Hz, 1 H) 7.00 - 7.10 (m, 3 H) 7.47 (d, J=1.77 Hz, 1 H) 7.99 (d, J=1.26 Hz, 1 H) 8.10 (s, 2 H) 8.21 (s, 1H) 8.92 (d, J=8.0 Hz, 1H).

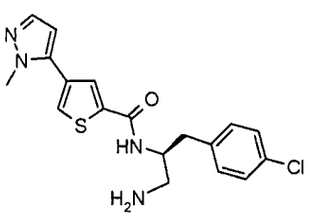
Example 77



Preparation of *N*-{(1*S*)-2-amino-1-[(3-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3-chlorophenyl)propyl]-*1H*-isoindole-1,3(2*H*)-dione (157 mg, 0.5 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.92 - 3.04 (m, 4 H) 3.92 - 3.98 (m, 3 H) 4.36 (d, J=5.56 Hz, 1 H) 6.47 (s, 1H) 7.19 - 7.29 (m, 2 H) 7.29 - 7.35 (m, 1 H) 7.37 - 7.42 (m, 1 H) 7.47 (s, 1H) 8.17 (s, 3 H) 8.85-9.07 (m, 1H).

Example 78

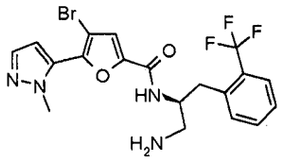


Preparation of *N*-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (104 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(4-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (157 mg, 0.5

mmol) [prepared according to the procedure of Preparation 6] for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione-HCl: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.92 - 2.97 (m, 2 H) 2.99 - 3.04 (m, 2 H) 4.01 (s, 3 H) 4.32 - 4.42 (m, 1 H) 6.43 - 6.50 (m, 1 H) 7.27 - 7.37 (m, 4 H) 7.47 (d, J=1.77 Hz, 1 H) 7.99 (d, J=1.26 Hz, 1 H) 8.21 (s, 3 H) 8.94-9.10 (m, 1H).

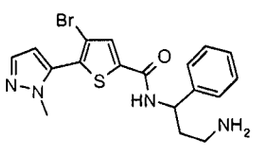
Example 79



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 6, except substituting 4,5-dibromo-2-furancarboxylic acid (135 mg, 0.5 mmol) for 5-bromo-2-thiophenecarboxylic acid: LC-MS (ES) m/z 472 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 3.11 (d, J=9.85 Hz, 1 H) 3.21 - 3.31 (m, 3 H) 4.06 (s, 3 H) 4.70 (s, 1 H) 6.87 (d, J=2.02 Hz, 1 H) 7.33 (s, 1 H) 7.41 - 7.48 (m, 1 H) 7.50 - 7.57 (m, 2 H) 7.60 (d, J=2.02 Hz, 1 H) 7.71 (d, J=7.83 Hz, 1 H).

Example 80



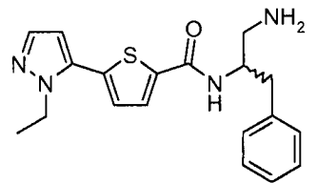
Preparation of *N*-(3-amino-1-phenylpropyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 1,1-dimethylethyl [3-(methylamino)-3-

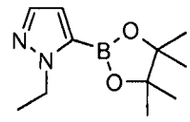
phenylpropyl]carbamate (125 mg, 0.5 mmoles) [from Preparation 3] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 420 $(M+H)^+$, ^1H NMR (400 MHz, DMSO) δ ppm 2.25 - 2.37 (m, 2 H) 2.96 (d, J=8.08 Hz, 1 H) 3.04 - 3.13 (m, 1 H) 3.84 (s, 3 H) 5.22 (t, J=7.58 Hz, 1 H) 6.53 (d, J=1.52 Hz, 1 H) 7.35 (d, J=6.57 Hz, 1 H) 7.44 (dt, J=15.09, 7.48 Hz, 4 H) 7.58.

Example 81

Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



a) 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole

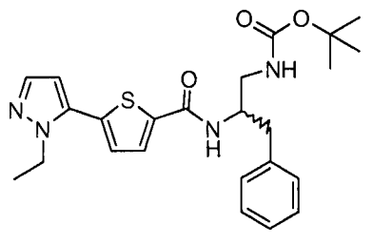


To a suspension of NaH (60% in mineral oil, 2.2 g, 55 mmol) in THF (50 mL) was added pyrazole (3.4 g, 50 mmol) in THF (10 mL) at room temperature. After 30 min, to above suspension was added EtI (7.75 g, 50 mmol) dropwise. After the reaction was complete (20 h), the suspension was filtered, and the resulting solution was used directly with further purification.

At 0°C, to above solution of 4-methyl pyrazole (~50 mmol) was added n-BuLi (2.5M in hexane, 22 mL, 55 mmol). The reaction solution was stirred for 1 hour at RT and then cooled to -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (10.2 g, 55 mmol). After 15 min at -78°C, the reaction was allowed to warm to 0°C over 1hour. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford a tan solid (9.8 g, 89%) which was used without further purification. LCMS (ES) m/z 141 $(M+H)^+$ for $[RB(OH)_2]$; ^1H NMR ($CDCl_3$, 400 MHz) δ ppm 7.52 (d, J =

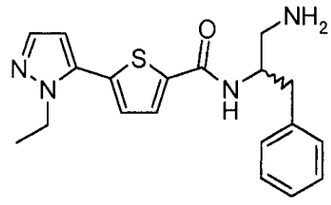
2 Hz, 1H), 6.36 (d, J = 2 Hz, 1H), 4.48 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2Hz, 3H), 1.36 (s, 12 H)

b) 1,1-dimethylethyl [2-({[5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (100 mg, 0.23 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (100 mg, 0.72 mmol), tetrakistriphenylphosphine Pd(0) (30 mg, 26 µmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (64 mg, 0.29 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 12h, the reaction mixture was concentrated under vacuum and purified on silica (hex/EtOAc, 40-60%) to afford the title compound (0.074 g, 71%) as a light yellow solid: LC-MS (ES) m/z 455 $(M+H)^+$.

c) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

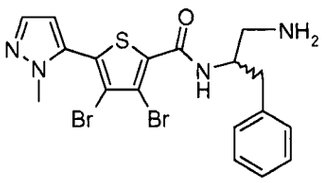


1,1-Dimethylethyl [2-({[5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (74 mg, 0.16 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). After 1 h, the solution was concentrated and neutralized through silica using 4% MeOH in DCM (1% NH_4OH). The title compound was further purified using reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%) affording the bis-TFA salt of the title compound (47 mg, 50%) as a white solid: LCMS (ES) m/z 355 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.71 (d, J = 3.8 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 7.34-7.22 (m, 6H), 6.51 (d. J = 1.8 Hz, 1H), 4.55

(m, 1H), 4.34 (q, J = 7.1 Hz, 2H), 3.22 (dd, J = 3.5, 13.1 Hz, 1H), 3.13 (dd, J = 10.1, 13.1 Hz, 1H), 3.00 (m, 2H), and 1.42 (t, J = 7.1 Hz, 3H).

Example 82

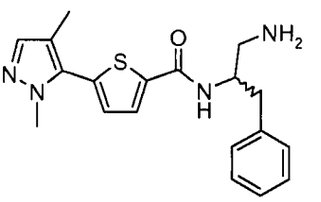
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,1-dimethylethyl (3-phenyl-2-{[(3,4,5-tribromo-2-thienyl)carbonyl]amino}propyl)carbamate (120 mg, 0.20 mmol) for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate: LC-MS (ES) m/z 499 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.59 (d, J = 2.0 Hz, 1H), 7.37-7.24 (m, 5H), 6.53 (d, J = 2.0 Hz, 1H), 4.62 (m, 1H), 3.27 (d, J = 13.1, 4.3 Hz, 1H), 3.21 (dd, J = 13.1, 9.4 Hz, 1H), 3.09 (dd, J = 14.2, 6.1 Hz, 1H), 3.02 (dd, J = 13.9, 9.1 Hz, 1H), and 1.96 (s, 3H).

Example 83

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



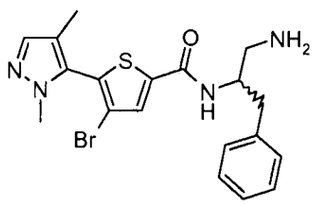
a) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-

1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (64.0 mg, 0.23 mmol) [from Preparation 17] for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate, and substituting 1,1-dimethylethyl (2-{[(5-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (110 mg, 0.25 mmol) for 1,1-dimethylethyl (2-{[(5-bromo-3-thienyl)carbonyl]amino}-2-phenylethyl)carbamate: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.75 (d, J= 3.8 Hz, 1H), 7.40 (br s, 1H), 7.32-7.23 (m, 5H), 7.21 (d, J = 3.8 Hz, 1H), 4.56 (m, 1H), 3.86 (s, 3H), 3.23 (dd, J = 13.1, 3.8 Hz, 1H), 3.15 (dd, J = 12.9, 10.1 Hz,1H), 3.01 (m, 2H) and 2.10 (s, 3H).

Example 84

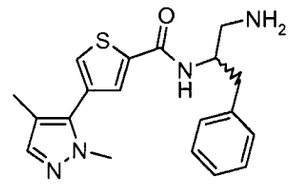
N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (77 mg, 0.23 mmol) [from Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, and substituting 1,1-dimethylethyl (2-{[(4,5-dibromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (150 mg, 0.29 mmol) for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate: LC-MS (ES) m/z 434 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.77 (s, 1H), 7.43 (s, 1H), 7.35-7.23 (m, 5H), 4.55 (m, 1H), 3.72 (s, 3H), 3.23 (dd, J = 3.5 Hz, 1H), 3.13 (dd, J = 10.6, 13.1 Hz, 1H), 3.02 -2.95 (m, 2H), and 1.99 (s, 3H).

Example 85

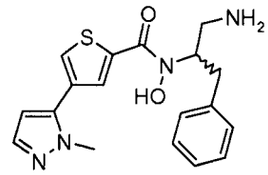
N-[2-amino-1-(phenylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



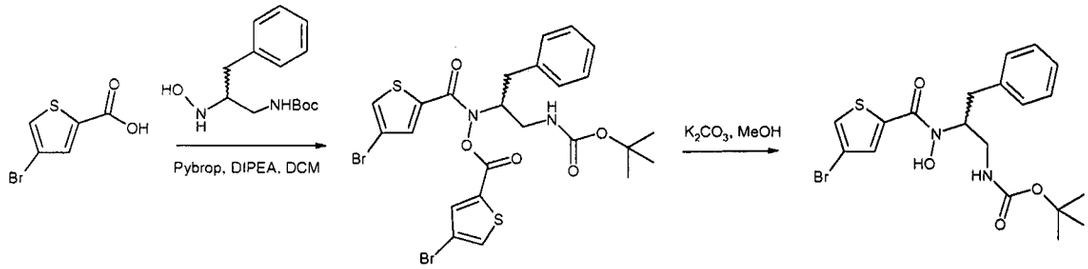
The title compound was prepared as a yellow solid according to the procedure of Example 1, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (220 mg, 1.0 mmol) [from Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole, and substituting 1,1-dimethylethyl (2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (150 mg, 0.34 mmol) for 1,1-dimethylethyl [2-({[4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furanyl]carbonyl}amino)-3-phenylpropyl]carbamate: LC-MS (ES) m/z = 355 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.14-8.13 (m, 3H), 7.35-7.20 (m, 5H), 4.58 (m, 1H), 4.07 (s, 3H), 3.36-3.22 (m, 2H), 3.12-3.01 (m, 2H), and 2.21 (s, 3H).

Example 86

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



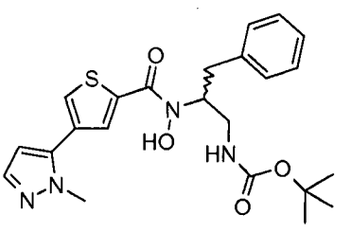
a) 1,1-dimethylethyl {2-[[(4-bromo-2-thienyl)carbonyl](hydroxy)amino]-3-phenylpropyl}carbamate



To a solution of 4-bromo-2-thiophenecarboxylic acid (1.0 g, 4.83 mmol) in DCM (10 mL) was added PyBrop (3.4 g, 7.24 mmol) and Hunig's base (2 mL, 12.6 mmol). After 15 min, 1,1-dimethylethyl [2-(hydroxyamino)-3-phenylpropyl]carbamate (641 mg, 2.41 mmol) was added to the reaction mixture in DCM (2 mL) and stirred for 2h at RT. The reaction solution was concentrated to give crude 1,1-dimethylethyl [2-([(4-bromo-2-thienyl)carbonyl]{[(4-bromo-2-thienyl)carbonyl]oxy}amino)-3-phenylpropyl]carbamate. LC-MS (ES) m/z = 645 $(M+H)^+$.

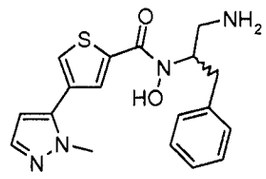
To a solution of 1,1-dimethylethyl [2-([(4-bromo-2-thienyl)carbonyl]{[(4-bromo-2-thienyl)carbonyl]oxy}amino)-3-phenylpropyl]carbamate in MeOH (5 mL) was added K_2CO_3 (1.0 g, 7.3 mmol). The mixture was stirred at RT for 2h. The mixture was concentrated under vacuum and purified on silica gel (EtOAc/Hexane, 30%) to give the the title compound (410 mg, 37 % for two steps) as an off white solid: LC-MS (ES) m/z = 456 $(M+H)^+$.

b) 1,1-dimethylethyl [2-(hydroxy{[4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 1,1-dimethylethyl {2-[[(4-bromo-2-thienyl)carbonyl](hydroxy)amino]-3-phenylpropyl}carbamate (100 mg, 0.22 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (91 mg, 0.66 mmol), tetrakistriphenylphosphine Pd(0) (23 mg, 0.022 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (68 mg, 0.33 mmol). The reaction mixture was heated to 75° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-40%) to afford the title compound (87 mg, 87%).: LC-MS (ES) m/z = 456 $(M+H)^+$.

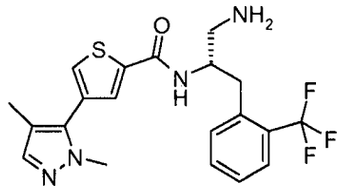
c) *N*-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



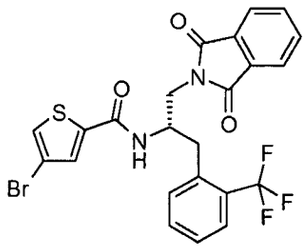
1,1-Dimethylethyl [2-(hydroxy{[4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (84 mg, 0.19 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). The reaction was stirred over 1h, and concentrated, and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40 -10%), and concentrated to afford the bis-TFA salt of the title compound (51.2 mg, 64.8%). LC-MS (ES) m/z 357 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.03 (s, 1H), 7.94 (d, J = 1.8Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 7.34-7.18 (m, 5H), 5.16 (m, 1H), 3.95 (s, 3H), 3.38 (dd, J = 13.1, 10.6 Hz, 1H), 3.17-3.11 (m, 2H), and 2.95 (dd, J = 13.6, 6.6 Hz, 1H)

Example 87

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

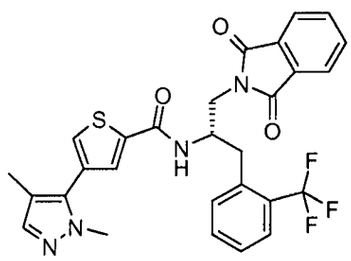


a) 4-bromo-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



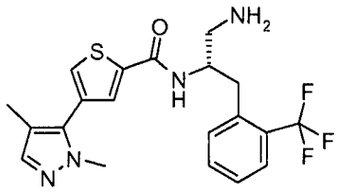
Ta a solution of 4-bromo-2-thiophenecarboxylic acid (80 mg, 0.39 mmol) in DCM (2 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (218 mg, 0.47 mmol) in one portion, followed by addition of DIPEA (0.2 mL, 1.14 mmol). After stirring for 10 min, diamine 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (165mg, 0.43 mmol) was added to above solution. After 2h, the solution was concentrated and purified via column chromatography (silica, 10% MeOH in CH_3Cl) affording the title compound (206 mg, 99%) as a white solid: LC-MS (ES) m/z 538 $(M+H)^+$.

b) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 4-bromo-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (200 mg, 0.37 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (0.17g, 1.23 mmol), tetrakistriphenylphosphine Pd(0) (42 mg, 0.036mmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (413 mg, 1.86 mmol) [from Preparation 17] . The reaction mixture was heated to 80° C in a sealed tube for 2h. The reaction solution was concentrated under vacuum, and purified on silica gel (10-50% EtOAc/Hex) to give the title compound (192 mg, 94%) as a white solid: LC-MS (ES) m/z 553 $(M+H)^+$.

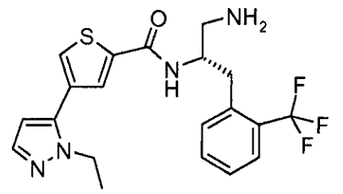
c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



4-(1,4-Dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (110 mg, 0.198 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.5 mL, 15.93 mmol). The reaction was stirred over 10 h, concentrated and the residue in DCM (2 mL) was treated with TFA (1.0 mL). After stirring for 2 h, the solvent was removed and the residue was purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%), and concentrated to afford the bis-TFA salt of the title compound. The bis-TFA salt was neutralized through a silica plug (90:9:1 $CHCl_3$/MeOH/NH_4OH) affording the free base of the title compound. The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (62 mg, 34.6%) as the HCl salt: LC-MS (ES) m/z 423 $(M+H)^+$, ^1H NMR (d4-MeOD, 400 MHz) δ ppm 8.27 (s, 1H), 8.22 (s, 1H), 8.18 (s, 1H), 7.70 (d, 7.8 Hz,1H), 7.64 (d, J = 7.6 Hz,1H), 7.51 (dd, J = 7.3, 7.3 Hz, 1H), 7.41 (dd, J = 7.6, 7.3 Hz, 1H), 4.69 (m, 1H), 4.12 (s, 3H), 3.41-3.19 (m, 4H), and 2.24 (s, 3H).

Example 88

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

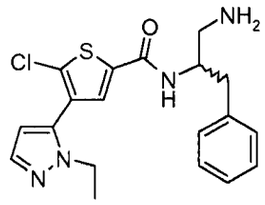


The title compound was prepared as a white solid according to the procedure of Example 87, except substituting 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (104 mg, 0.47 mmol) for 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole. LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.35-8.31 (m, 2H), 8.21 (br s, 1H), 7.70 (d, J =

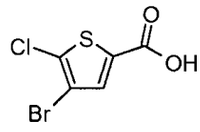
7.8 Hz, 1H), 7.64 (d, J = 7.3 Hz, 1H), 7.51 (dd, J = 7.3, 7.3 Hz, 1H), 7.42 (dd J = 7.6, 7.3 Hz, 1H), 7.00 (m, 1H), 4.70-4.61 (m, 3H), 3.40-3.17 (m, 4H), and 1.57 (t, J = 6.8 Hz, 3H).

Example 89

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

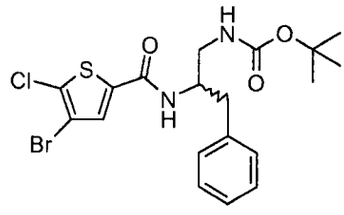


a) 5-chloro-4-methyl-2-thiophenecarboxylic acid



To a solution of 4-bromo-2-thiophenecarboxylic acid (2.07 g, 10 mmol) in DMF (5 mL) was added NCS (2.7 g, 15 mmol) in one portion. The reaction mixture was stirred at 50 °C for 10 h, and then cooled to room temperature. The desired product precipitated after water (5 mL) was added. The white solid was filtered and dried under high vacuum to give 1.9 g (79%). LC-MS (ES) m/z =242 $(M+H)^+$,

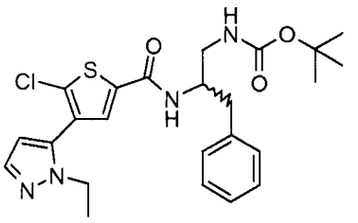
b) 1,1-dimethylethyl (2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate



To a solution of 5-chloro-4-methyl-2-thiophenecarboxylic acid (242 mg, 1.0 mmol) and diisopropylethyl amine (2.5 mL, 14.60 mmol) in DCM (50 mL) at 25 °C

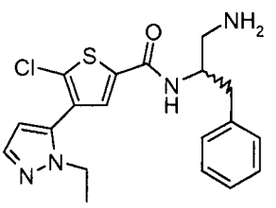
was added PyBrOP (2.5 g, 5.30 mmol) in one portion. After 30 min, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (250 mg, 1.0 mmol) was added at one portion. After 2h, the solution was concentrated and purified via column chromatography (silica, 10-40% EtOAc in Hexane) affording the title compound (460 mg, 97%) as a white solid: LC-MS (ES) m/z = 474 $(M+H)^+$.

c) 1,1-dimethylethyl [2-({[5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of 1,1-dimethylethyl (2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (100 mg, 0.21 mmol) in THF (5 mL) was added Na_2CO_3 (2N, 0.3 mL, 0.6 mmol), $Pd(dppf)Cl_2$ (20 mg, 24 µmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (92 mg, 0.42 mmol). The reaction mixture was heated to 80 °C in a sealed tube under N_2. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (hex/EtOAc, 20-50%) to afford the title compound (74 mg, 72%) as a light yellow solid: LC-MS (ES) m/z 489 $(M+H)^+$.

d) *N*-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

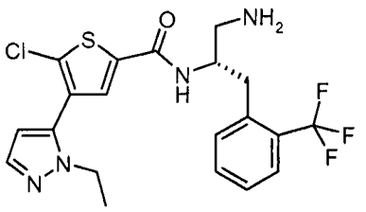


1,1-dimethylethyl [2-({[5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (61 mg, 0.12 mmol) was dissolved in DCM (2 mL) and treated with TFA (1 mL). After 0.5h, the solution was concentrated and neutralized through silica using 4% MeOH in DCM (1% NH_4OH).

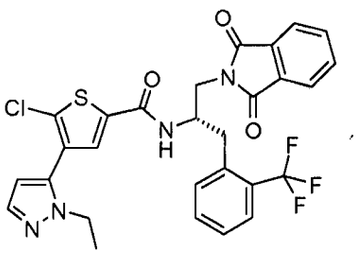
The title compound was further purified using reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%) affording the bis-TFA salt of the title compound (41 mg, 53%) as a white solid. LC-MS (ES) m/z = 389 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.61(d, J = 2.0Hz, 1H), 7.59 (s, 1H), 7.33-7.21 (m, 5H), 6.41 (d, J = 2.0Hz, 1H), 4.52 (m, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.22 (dd, J = 12.9, 3.5 Hz, 1H), 3.12 (dd, J = 12.6, 10.1 Hz, 1H), 2.98 (m, 2H), and 1.35 (t, J = 7.1Hz, 3H).

Example 90

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

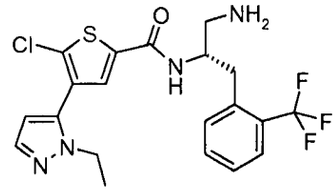


a) 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 89(c), except substituting 4-bromo-5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (150 mg, 0.26 mmol) for 1,1-dimethylethyl (2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate: LC-MS (ES) m/z 587 $(M+H)^+$.

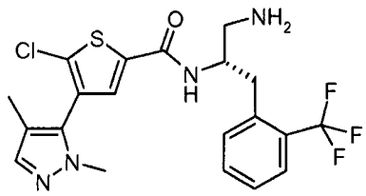
b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



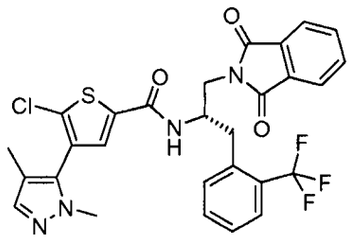
To a solution of 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (110 mg, 0.19 mmol) in MeOH/THF(5 mL/0.5 mL) was added hydrazine (0.5 mL, 15.9 mmol). After stirring overnight at RT, the reaction mixture was concentrated, and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water, and neutralized by ammonium hydroxide. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4, and concentrated to give a free base of the title compound, which was dissolved in MeOH (2 mL), and treated with HCl (aq, 37%). After stirring overnight, the reaction solution was concentrated to give the title compound (26 mg, 26 %) as a di-HCl salt: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 8.28 (d, J = 2.5Hz, 1H), 8.07 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.53 (dd, J = 7.3, 7.6 Hz, 1H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 6.90 (d, J = 2.5 Hz, 1H), 4.66 (m, 1H), 4.43 (q, J = 7.3 Hz, 2H), 3.37-3.16 (m, 4H), and 1.50 (t, J = 7.3 Hz, 3H).

Example 91

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

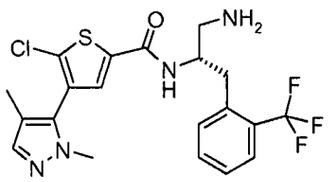


a) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 4-bromo-5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (260 mg, 0.46 mmol) in THF (5 mL) was added Na_2CO_3 (2N, 0.7 mL, 1.4 mmol), $Pd(dppf)Cl_2$ (40 mg, 48 µmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (303 mg, 1.38 mmol). The reaction mixture was heated to 75 °C in a sealed tube under N_2. After 8h, the reaction mixture was concentrated under vacuum and purified on silica (10:1 CHCl3/MeOH) to afford the title compound (196 mg, 73.4%): LC-MS (ES) m/z = 587 $(M+H)^+$.

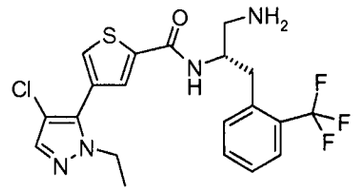
b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



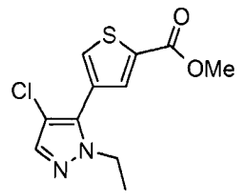
To a solution of 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (196 mg, 0.34 mmol) in MeOH/THF(2 mL/0.5 mL) was added hydrazine (0.5 mL, 15.9 mmol). After stirring overnight at RT, the reaction mixture was concentrated, and purified on silica (50% MeOH in $CHCl_3$ (0.5% NH_4OH) to give a free base of the tile compound, which was dissolved in MeOH (2 mL), and treated with HCl (aq, 37%). After stirring overnight, the reaction solution was concentrated to give the title compound (107 mg, 51 %) as a di-HCl salt: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.96 (s, 1H), 7.90 (m, 1H), 7.70 (d, J =7.6 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.53 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 4.66 (m, 1H), 3.91 (s, 3H), 3.33-3.14 (m, 4H), and 2.10 (s, 3H).

Example 92

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



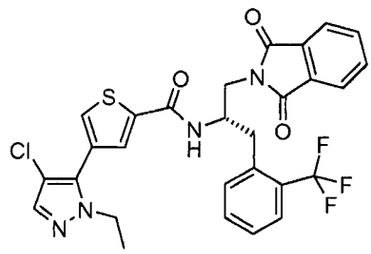
a) methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (1.0 g, 4.52 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (1.86 g, 13.5 mmol), tetrakistriphenylphosphine Pd(0) (260 mg, 0.23 mmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole(1.3 g, 5.85 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (hex/EtOAc, 20-40%) to afford methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.7 g, 66%) as a light yellow solid: LC-MS (ES) m/z = 237 $(M+H)^+$.

To a solution of the above compound (0.5 g, 2.11 mmol) in THF (10 mL) was added NCS (0.364g, 2.74 mmol). The reaction mixture was heated to 70° C under nitrogen. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (Hexanes/EtOAc, 10-20%) to afford the title compound (0.45 g, 78%) as a light yellow solid: LC-MS (ES) m/z 271 $(M+H)^+$.

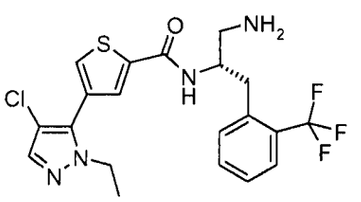
(b) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.3 g, 1.1 mmol) in THF/H_2O (5 mL/0.5 mL) was added KOH (0.2 g, 3.4 mmol). The reaction mixture was heated to 50° C for 4 h and then concentrated and diluted with H_2O (2 mL). The pH was adjusted to 3 with aqueous HCl. The mixture was extracted with DCM (3 x 5 mL) and the collected organic fractions were concentrated under vacuum to give crude 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (260 mg) which was used directly without further purification. LC-MS (ES) m/z = 256 $(M+H)^+$.

To a solution of 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (0.26 g, 1.0 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (0.35 g, 1.1 mmol) and DIPEA (0.5 mL, 2.86 mmol) in DCM (5 mL) at 25 °C was added PyBrOP (0.6 g, 1.2 mmol) in one portion. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/hexane) affording the title compound (0.54 g, 91%) as a white solid: LC-MS (ES) m/z = 588 $(M+H)^+$.

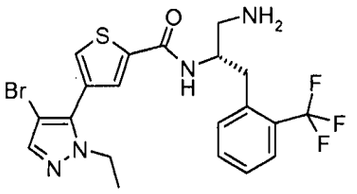
c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



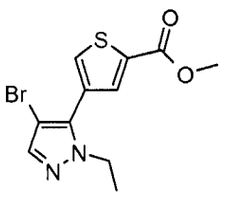
4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (350 mg, 0.60 mmol) was dissolved in MeOH (5 mL) and treated with NH_2NH_2 (0.5 mL,15.93 mmol). The mixture was stirred at RT overnight, and concentrated. The residue was purified by column chromatography (silica, 2-5% MeOH in $CHCl_3$ (0.5% NH_4OH) affording the free base of the title compound, which was treated with HCl(aq) in MeOH to give title compound (0.16 g, 51%) as a off white solid: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.97- 7.94 (m, 2H), 7.71 (d, J = 7.8 Hz, 1H), 7.61 (s, 1H), 7.56-7.51 (m, 2H), 7.43 (dd, J = 7.6, 7.6 Hz, 1H), 4.67 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.36-3.12 (m, 4H), and 1.38 (t, J = 7.1 Hz, 3H).

Example 93

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

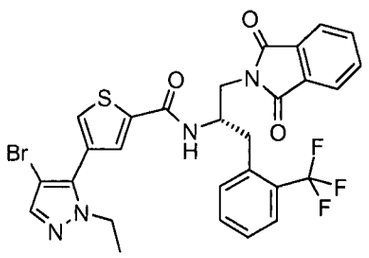


a) methyl 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.45 g, 1.9 mmol) [see example 92(a)] in THF (5 mL) was added NBS (0.33 g, 2.5 mmol). The reaction mixture was heated to 70° C under nitrogen. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/hexanes, 10-30%) to afford the title compound (0.47 g, 78%). LC-MS (ES) m/z = 316 $(M+H)^+$.

b) 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide

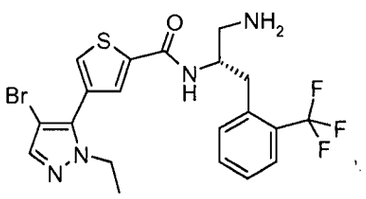


To a solution of methyl 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (0.2 g, 0.63 mmol) in THF/H_2O (5 mL/1 mL) was added KOH (0.15 g, 2.4 mmol). The reaction mixture was heated to 50° C for 10h and then

concentrated and diluted with H_2O (2 mL). The pH was adjusted to 6 with aqueous HCl. The mixture was extracted with DCM (3 x 5 mL) and the collected organic fractions were concentrated under vacuum to give crude 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid, which was used directly without further purification. LC-MS (ES) m/z = 302 $(M+H)^+$.

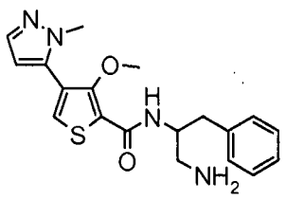
To a solution of 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid 156 mg, 0.52 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (0.18 g, 0.52 mmol) and DIPEA (0.5 mL, 2.86 mmol) in DCM (5 mL) at 25 °C was added PyBrOP (0.29g, 0.62 mmol) in one portion. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-60 % EtOAc/hexane) affording the title compound (0.281 g, 86%). LC-MS (ES) m/z = 632 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



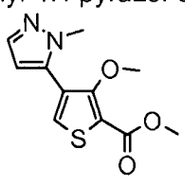
4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (250 mg, 0.39 mmol) was dissolved in MeOH (5 mL) and treated with NH_2NH_2 (0.5 mL, 15.93 mmol). The mixture was stirred at RT overnight, and concentrated. The residue was purified by column chromatography [silica, 2-10% MeOH in $CHCl_3$ (0.5% NH_4OH)] affording the free base of the title compound, which was treated with HCl(aq) in MeOH to give the title compound (144 mg, 51%) as an off white solid: LC-MS (ES) m/z 502 $(M+H)^+$. ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.93-7.87 (m, 2H), 7.72 (d, J = 8.1 Hz, 1H), 7.62 (s, 1H), 7.57-7.51 (m, 2H), 7.43 (t, J = 6.6 Hz, 1H), 4.67 (m, 1H), 4.25 (q, J = 7.3 Hz, 2H), 3.37-3.11(m, 4H), and 1.37 (t, J = 7.1Hz, 3H).

Example 94



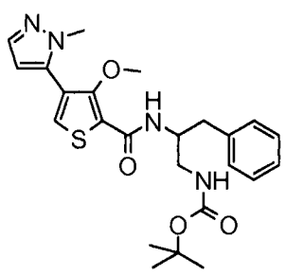
Preparation of *N*-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



Methyl 4-bromo-3-(methyloxy)-2-thiophenecarboxylate (250 mg, 0.10 mmol) [prepared according to Corral, C.; El-Ashmawy, M.B.; Lissavetzky, J.; Basilio, A.; Giraldez, A.; *Eur. J. Med. Chem. Chim. Ther.* 22; **1987**; 251-254.], 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (250 mg, 1.20 mmol), $Pd(PPh_3)_4$ (58 mg, 49.8 μmol) and K_2CO_3 (550 mg, 3.98 mmol) in dioxane (5 mL) and H_2O (1 mL) were combined in a sealed tube. After 12h at 80 °C, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 0.5 % MeOH in DCM) affording the title compound (215 mg, 86%) as a brown residue: LCMS (ES) m/z = 253 $(M+H)^+$.

b) 1,1-dimethylethyl [2-({[3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



i) A solution of methyl 3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (215 mg, 0.853 mmol) in 6N NaOH (4 mL) and THF (4 mL) was stirred in a sealed tube at 70 °C. After 2h, the solution was acidified to pH 3

using 1N HCl then extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 239 $(M+H)^+$.

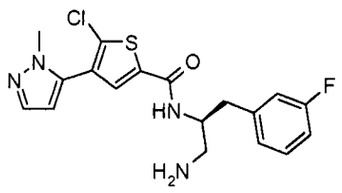
ii) To a solution of the crude acid, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (210 mg, 0.844 mmol) [from Preparation 2] and diisopropylethyl amine (735 µL, 4.22 mmol) in DCM (8 mL) was added PyBrop (472 mg, 1.01 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly: LCMS (ES) m/z = 471 $(M+H)^+$.

c) N-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

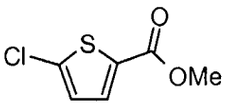
A solution of 1,1-dimethylethyl [2-({[3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from part b) in TFA-DCM (3 mL, 1:2) was stirred at 25 °C. After 30min, the solution was concentrated with a toluene azeotrope and the residue neutralized through a silica plug (3% MeOH in DCM (1% NH_4OH)) affording the free base of the title compound.

The free base, as a solution in MeOH, was then treated with excess 4M HCl in dioxane affording the title compound (270 mg, 86%-2steps) as the HCl salt: LCMS (ES) m/z 371 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.06 (br. s., 3 H) 7.91 (s, 1 H) 7.72 (d, J=8.59 Hz, 1 H) 7.52 (d, J=1.77 Hz, 1 H) 7.25 - 7.31 (m, 4 H) 7.18 - 7.23 (m, 1 H) 6.39 (d, J=2.02 Hz, 1 H) 4.52 (br. s., 1 H) 3.78 (s, 3 H) 3.41 (s, 3 H) 2.97 - 3.05 (m, 4 H).

Example 95



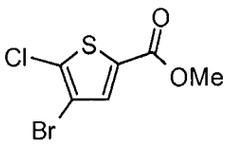
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



a) methyl 5-chloro-2-thiophenecarboxylate

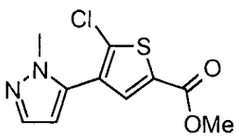
To a solution of 5-chloro-2-thiophenecarboxylic acid (20 g, 123 mmoles) in MeOH (200 mL) was added conc. H_2SO_4 (5 mL). After heating to 55°C for 12 h, the reaction solution was concentrated and diluted with DCM (250 mL). The DCM solution was washed with aqueous $NaHCO_3$, then H_2O and dried over Na_2SO_4. Concentration under vacuum gave the title compound as a yellow oil (21.5 g, 99%): LCMS (ES) m/z 178 $(M+H)^+$.

b) methyl 4-bromo-5-chloro-2-thiophenecarboxylate



To a 1 L round bottom flask was added aluminum chloride (11.32 g, 85 mmol) and methyl 5-chloro-2-thiophenecarboxylate (10 g, 56.6 mmol) dissolved in $CHCl_3$ (250 mL). Br_2 (4.08 ml, 79 mmol) was added dropwise over 10 minutes. After stirring for 6 h at 25 °C, the light orange reaction solution was washed with sat $NaHCO_3$. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [hexanes/EtOAc, 9:1] to give the product [12 g, 80%] as a white solid. LCMS (ES) m/z 256 $(M+H)^+$.

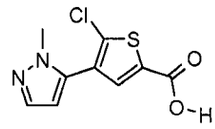
c) methyl 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 300 mL sealed flask was added 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (8.14 g, 39.1 mmol), potassium carbonate (12.98 g, 94 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (8 g, 31.3 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.40 g, 0.78 mmol) in 1,4-dioxane (50 ml) and H_2O (6 ml). After stirring for 90 min at 75 °C, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered

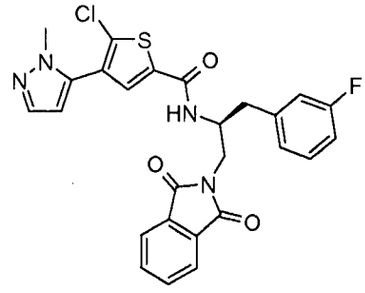
and concentrated. The reaction residue was purified on silica gel [hexanes/EtOAc, 2:1] to give the product [5.7 g, 70%] as a tan solid: LCMS (ES) m/z 258 $(M+H)^+$.

d) 5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 250 mL round-bottomed flask was added methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (4.4 g, 17.14 mmol) and sodium hydroxide (28.6 ml, 171 mmol) in tetrahydrofuran (THF) (50 ml) and MeOH (50 mL). The reaction solution was stirred at RT for 12h and then made acidic (pH ~ 2) with 2.5 M HCl and extracted with DCM. The organic layer was separated, dried (Na_2SO_4) and concentrated to an off-white solid (4.2 g, 94%) which was used directly without further purification: LCMS (ES) m/z 243 $(M+H)^+$.

e) 5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



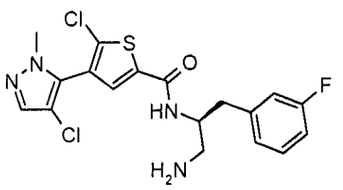
To a 500 mL round-bottomed flask was added 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (4.2 g, 17.31 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (6.37 g, 19.04 mmol) [prepared according to the procedure of Preparation 6], N,N-diisopropyl ethylamine (4.53 ml, 26.0 mmol) and Pybrop (12.05 g, 26.0 mmol) in dichloromethane (DCM) (150 ml). After stirring at RT for 12 h, the reaction solution was washed with H_2O (2 x 100mL) and the organic layer was dried Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with [EtOAc/hexanes, 1:1] to give the product [7.8 g, 86%] as a white solid: LCMS (ES) m/z 524 $(M+H)^+$.

f) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 250 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (7.8g, 14.91 mmol) and hydrazine (14.50 ml, 298 mmol) in tetrahydrofuran (THF) (75 ml) and methanol (75 mL). After 24 h at RT, the precipitate was filtered, the filtrate was concentrated. The crude product was purified on a silica gel column [$CHCl_3$/MeOH/NH_4OH, 90:9:1] to give the title compound as a white solid.

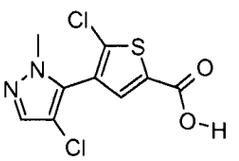
The free base product was treated with 4M HCl in dioxane (15 mL). After 5 min, the solution was concentrated and dried under vacuum to afford the product (6.8 g, 95%) as an HCl salt: LCMS (ES) m/z 467 $(M+H)^+$, ^1H NMR (400 MHz, CD3OD) δ ppm 7.97 (s, 2H), 7.31 (s, 1H), 7.14 (m, 2H), 6.98 (m, 1H), 6.75 (s, 1H), 4.54 (m, 1H), 3.98 (s, 3H), 3.24 (m, 2H), 3.04 (m, 2H).

Example 96



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

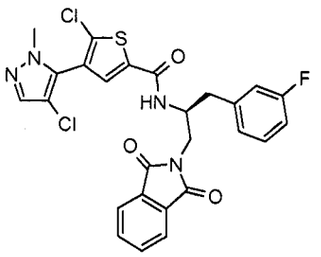
a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 500 mL flask was added methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (5 g, 19.48 mmol) [from Example 95] and NCS (3.12 g, 23.37 mmol) in tetrahydrofuran (THF) (100 ml) (50 mL). After stirring for 4 h at 70 °C, the yellow reaction solution was treated with 6M NaOH (32 mL, 195 mmole) and stirred an additional 2 hours. The reaction solution was diluted with H_2O (50 mL)

and DCM (200 mL). The organic layer was separated and the aqueous layer made acidic with 6N HCl. The acidic aqueous solution was extracted with DCM (3 x 200 mL), dried over Na_2SO_4, and concentrated to give the crude product [2.6 g, 48%] as a tan solid: LCMS (ES) m/z 277 $(M+H)^+$.

b) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



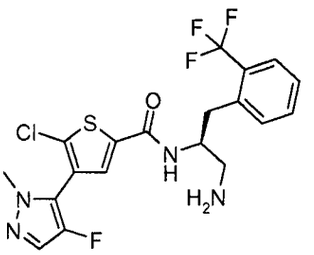
To a 500 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (6 g, 21.65 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (7.25 g, 21.65 mmol) [prepared according to the procedure of Preparation 6], N,N-diisopropyl ethylamine (5.67 ml, 32.5 mmol) and Pybrop (15.08 g, 32.5 mmol) in Dichloromethane (DCM) (150 ml). After stirring at RT for 12 h, the reaction solution was washed with H_2O (2 x 100mL) and the organic layer was dried Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with [EtOAc/hexanes, 1:1] to give the product [9.0g, 74%] as a white solid: LCMS (ES) m/z 558 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 250 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (9 g, 16.15 mmol) and hydrazine (15.69 ml, 323 mmol) in tetrahydrofuran (THF) (75 ml) and methanol (75 mL). After 24 h at RT, the precipitate was filtered, the filtrate was concentrated, and the crude product was purified on a silica gel column [$CHCl_3$/MeOH/NH_4OH, 90:9:1] to give the title compound as a white solid.

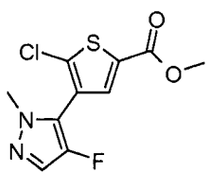
The free base product was treated with 4M HCl in dioxane (15 mL). After 5 min, the product solution was concentrated and dried under vacuum to afford the product (6.5 g, 91%) as an HCl salt: LCMS (ES) m/z 428 $(M+H)^+$; ^1H NMR (400 MHz, CD_3OD) δ ppm 7.75 (s, 1 H), 7.60 (s, 1H), 7.32 (m, 1H) 7.14 (m, 2H), 6.98 (m, 1H), 4.54 (m, 1H), 3.78 (s, 3H), 3.24 (m, 2H), 3.02 (m, 2H).

Example 97



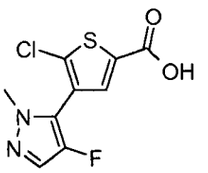
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



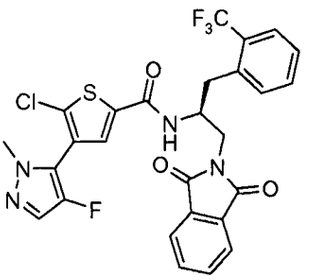
To a solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 0.974 mmol)[prepared according to the procedure in Example 95] in acetonitrile (4.864 ml) and H_2O (486 µl) was added selectfluor (449 mg, 1.27 mmol). The resulting solution was stirred at 70 °C in a sealed tube for 1h after which additional selectfluor (449 mg, 1.266 mmol) was added in one portion. After stirring 12h, the solution was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM-THF and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 10% EtOAc in hexanes) affording methyl 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (65 mg, 0.237 mmol, 24.30 % yield) as a yellow solid; LCMS (ES) m/z 274, 276 (M, M+H).

b) 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (65 mg, 0.237 mmol) in 6N sodium hydroxide (0.39 ml, 2.37 mmol) and tetrahydrofuran (2 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (54 mg, 0.17 mmol, 72 % yield) as a yellow oil; LCMS (ES) m/e 261, 263 (M, M+2)+.

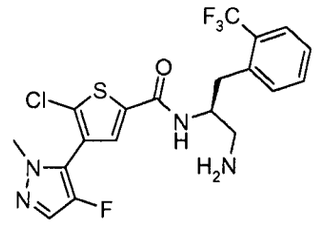
c) 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (53 mg, 0.203 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (78 mg, 0.203 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.18 ml, 1.02 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (95 mg, 0.203 mmol) in one portion. The solution stirred at 25 °C over 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40% EtOAc in hexanes) yielding 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-

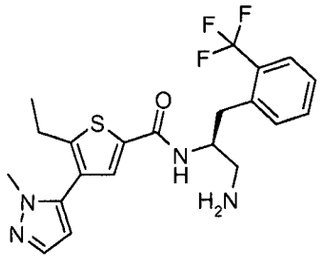
2-thiophenecarboxamide (106 mg, 0.129 mmol, 63.5 % yield) as a clear oil; LCMS (ES) m/e 591, 593 (M, M+H)+.

d) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



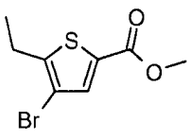
To a solution of 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (106 mg, 0.179 mmol) in tetrahydrofuran (1.095 ml) and methanol (1.095 ml) at 25 °C was added hydrazine (0.056 ml, 1.79 mmol) dropwise. After 48h, the solution was concentrated, dry loaded (silica, 5% MeOH in DCM (1% NH_4OH)) and purified initially by column chromatography. The residue was then further purified via gilson reverse phase chromatography using 2%-95% mobile phase affording the TFA salt of the title compound. This compound was neutralized through a plug of silica (5% MeOH in DCM (1% NH_4OH)) concentrated and transferred to the HCl salt adding excess 4M HCl in dioxane (500 ul) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (17 mg, 0.029 mmol, 16.16 % yield) as a white solid: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 9.11 (s,1 H) 8.11 (s, 1 H) 7.71 (br. s., 3 H) 7.66 - 7.70 (m, 2H) 7.54 - 7.61 (m, 2H) 7.41 - 7.44 (m, 1 H) 4.47 (br. s., 1 H) 3.79 (s, 3 H) 3.07 - 3.16 (m, 4 H).

Example 98



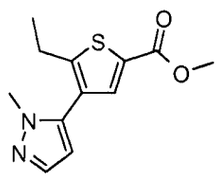
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-5-ethyl-2-thiophenecarboxylate



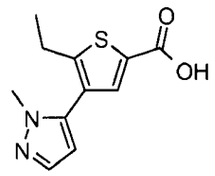
To a solution of 4-bromo-5-ethyl-2-thiophenecarboxylic acid (1 g, 4.25 mmol) in methanol (21.27 ml) was added sulfuric acid (0.23 mL, 4.25 mmol). The resulting solution was stirred at 50 °C for 48h. H_2O (50 mL) was added and the reaction was cooled to 0 °C in an ice-bath. The pH was adjusted to ~12 and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4-bromo-5-ethyl-2-thiophenecarboxylate (1.060 g, 4.25 mmol, 100 % yield): LCMS (ES) m/e 248, 250 (M, M+2)+.

b) methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



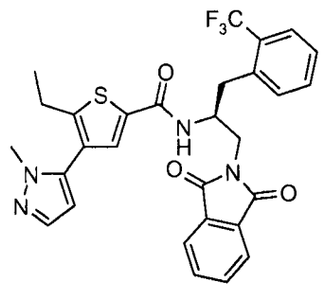
A solution of methyl 4-bromo-5-ethyl-2-thiophenecarboxylate (300 mg, 1.204 mmol), potassium carbonate (832 mg, 6.02 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (326 mg, 1.565 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (30.8 mg, 0.060 mmol) were combined in a sealed tube and stirred at 80 °C for 1h. The reaction contents were then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (301 mg, 1.204 mmol, 100 % yield) as a brown oil: LCMS (ES) m/e 251 $(M+H)^+$.

c) 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



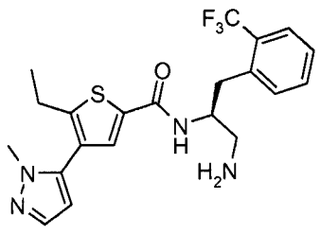
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.198 mmol) in 6N sodium hydroxide (2.397 ml, 1.198 mmol) and tetrahydrofuran (5.992 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (283 mg, 1.2 mmol, 100 % yield) as a yellow oil; LCMS (ES) m/z = 236 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



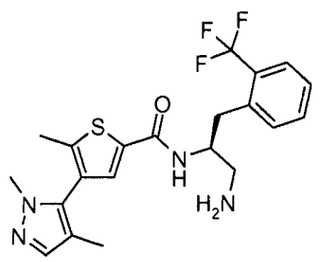
To a solution of 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (283 mg, 1.2 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (461 mg, 1.2 mmol)[prepared according to Preparation 6] and diisopropylethylamine (1.043 ml, 5.99 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (615 mg, 1.317 mmol) in one portion. The solution was stirred at 25 °C over 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (486 mg, 0.86 mmol, 71.6 % yield) as a clear oil: LCMS (ES) m/e 567 (M+H)+.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



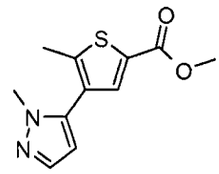
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (486 mg, 0.86 mmol) in tetrahydrofuran (2.144 ml) and methanol (2.14 ml) at 25 °C was added hydrazine (0.269 ml, 8.58 mmol) dropwise. After 12h, the solution was concentrated, dry loaded and purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)). The free base was then converted to the HCl salt by adding excess 4M HCl in dioxane (500 ul) to the residue in MeOH (2 ml) affording N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (250 mg, 0.491 mmol, 57.2 % yield)-2 HCl as a white solid: LCMS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d6) δ ppm 8.84 (d, J=8.84 Hz, 1 H) 8.08 (br. s., 3 H) 7.93 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.51-7.61 (m, 3 H) 7.39 - 7.46 (m, 1 H) 6.34 (d, J=2.02 Hz, 1 H) 4.48 (br. s., 1 H) 3.77 (s, 3 H) 2.99-3.11 (m, 4 H) 2.74 (q, J=7.49 Hz, 2 H) 1.16 (t, J=7.45 Hz, 3 H).

Example 99



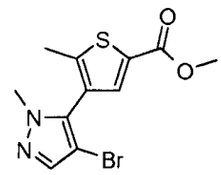
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



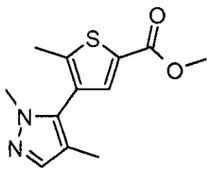
A solution of methyl 4-bromo-5-methyl-2-thiophenecarboxylate (2g, 8.51 mmol)[prepared in Preparation 10], potassium carbonate (5.88 g, 42.5 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.124 g, 10.21 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.217 g, 0.425 mmol) in 1,4-Dioxane (35.4 ml) and H_2O (7.09 ml) was stirred at 80 °C in a sealed tube for 1h. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 25% EtOAc in hexanes) affording methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate. This reaction was run in several batches (1g, 3 x 2g) which were combined for workup and purification affording the title compound (5.5 g, 78% combined yield) as a viscous yellow oil: LCMS (ES) m/e 236 $(M+H)^+$.

b) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



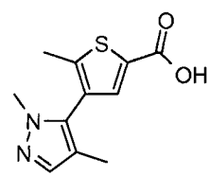
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (580 mg, 2.45 mmol) and n-bromosuccinimide (437 mg, 2.45 mmol) in tetrahydrofuran (12.300 ml) was stirred in a sealed tube for 1h at 70 °C. The solution was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAc in hexanes) yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (600 mg, 1.90 mmol, 78 % yield) as a yellow oil: LCMS (ES) m/e 314, 316 $(M, M+H)^+$.

c) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



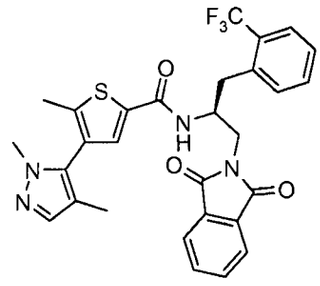
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (420 mg, 1.33 mmol), potassium carbonate (921 mg, 6.66 mmol), $PdCl_2$(dppf) (98 mg, 0.13 mmol) and trimethylboroxine (0.371 ml, 2.67 mmol) in N,N-dimethylformamide (6.663 ml) was stirred at 110 °C in a sealed tube for 2h. This reaction was run in two batches (100 mg and 420 mg) which were combined and partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (240 mg, 58%) as a yellow oil: LCMS (ES) m/e 251 $(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



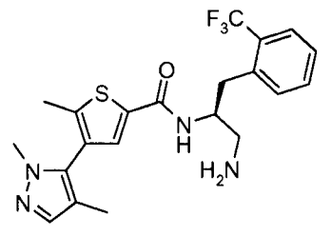
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (240 mg, 0.96 mmol) in 6N sodium hydroxide (3.20 ml, 19.18 mmol) and tetrahydrofuran (4.79 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (217 mg, 0.92 mmol, 96 % yield) as a yellow oil: LCMS (ES) m/e 236 $(M+H)^+$.

e) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



To a solution of methyl 4-methyl-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (217 mg, 0.918 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (353 mg, 0.92 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.800 ml, 4.59 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (472 mg, 1.01 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (373 mg, 0.66 mmol, 71.7 % yield) as a yellow foam: LCMS (ES) m/e 567 (M+H)+.

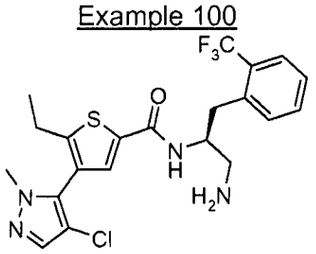
f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (373 mg, 0.66 mmol) in tetrahydrofuran (1.65 ml) and methanol (1.65 ml) at 25 °C was added hydrazine (0.21 ml, 6.58 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-

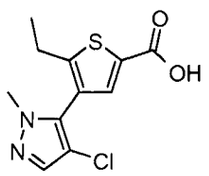
thiophenecarboxamide (253 mg, 0.497 mmol, 75 % yield) as a yellow solid: LCMS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d6) δ ppm 8.80 (d, J=8.59 Hz, 1 H) 8.09 (br. s., 3 H) 7.82 (s, 1 H) 7.69 (d, J=7.83 Hz, 1 H) 7.58 (t, J=8.08 Hz, 1 H) 7.43 (t, J=7.33 Hz, 1 H) 7.38 (s, 1 H) 4.47 (br. s., 1 H) 3.64 (s, 3 H) 2.99 - 3.07 (m, 4 H) 2.27 (s, 3 H) 1.89 (s, 3 H).

Example 100



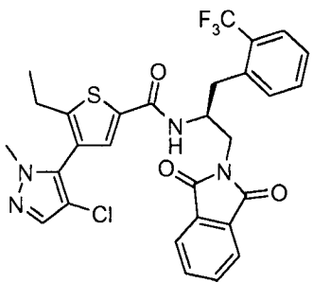
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



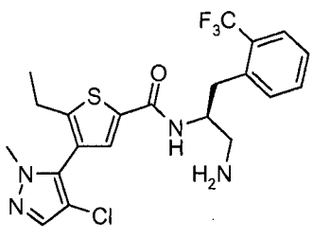
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.2 mmol)[Prepared in Example 98] and N-chlorosuccinimide (160 mg, 1.2 mmol) in tetrahydrofuran (6 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (1 ml, 5.99 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAC in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (325 mg, 1.20 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 271, 273 $(M, M+2)^+$.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (200 mg, 0.74 mmol), N,N-diisopropylethylamine (0.64 ml, 3.69 mmol) and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (284 mg, 0.74 mmol)[prepared according to Preparation 6] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (414 mg, 0.886 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (316 mg, 0.526 mmol, 71 % yield) as a white foam: LCMS (ES) m/e 601, 603 $(M, M+2)^+$.

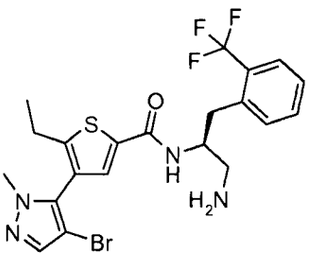
c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (316 mg, 0.53 mmol) in tetrahydrofuran (1.314 ml) and methanol (1.3 ml) at 25 °C was added hydrazine (0.16 ml, 5.26 mmol) dropwise. After 12h, the solution was concentrated, purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)) and converted to the HCl salt by adding excess 2M HCl in Et_2O (2 ml) to the residue in MeOH (5 ml) affording the HCl salt of

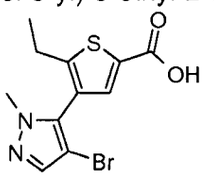
N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide (163 mg, 0.30 mmol, 57 % yield) as a white solid: LCMS (ES) m/z = 471, 473 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.82 (br. s., 1 H) 8.04 (bs, 3 H) 7.85 (s, 1 H) 7.65 - 7.72 (m, 2 H) 7.52-7.59 (m, 2 H) 7.39 - 7.46 (m, 1 H) 4.41-4.47 (m, 1 H) 3.71 (s, 3 H) 2.98-3.07 (m, 4H) 2.67 (q, J=7.58 Hz, 2 H) 1.16 (t, J=7.58 Hz, 3 H).

Example 101



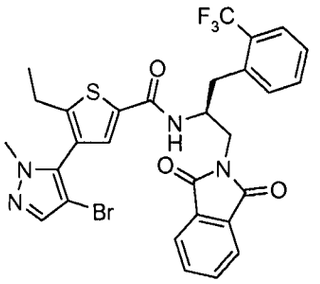
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



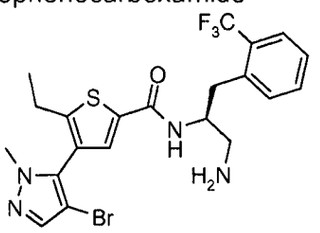
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.2 mmol)[Prepared in Example 98] and N-bromosuccinimide (213 mg, 1.2 mmol) in Tetrahydrofuran (5.99 ml) was stirred in a sealed tube for 1h at 70 °C. Aqueous sodium hydroxide (4.0 ml, 23.97 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAC in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (378 mg, 1.2 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 314, 316 (M, M+2)$^+$.

b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (200 mg, 0.57 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (181 mg, 0.57 mmol)[Prepared according to Preparation 6] and N,N-diisopropylethylamine (0.50 ml, 2.87 mmol) in Dichloromethane (4.23 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (295 mg, 0.632 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (240 mg, 0.37 mmol, 64.8 % yield) as a white foam: LCMS (ES) m/e 645, 647 $(M, M+2)^+$.

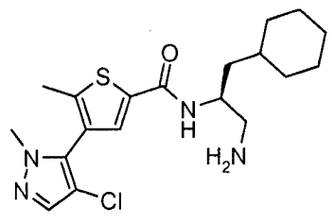
c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (240 mg, 0.37 mmol) in tetrahydrofuran (1.31 ml) and methanol (1.31 ml) at 25 °C was added hydrazine (0.12 ml, 3.72 mmol) dropwise. After 12h, the solution was concentrated, purified via column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)) and converted to the HCl salt by adding

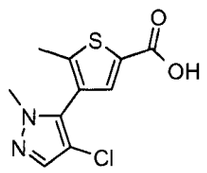
excess 4M HCl in dioxane (2 ml) to the residue in MeOH (5 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide (167 mg, 0.28 mmol, 76 % yield) as a white solid: LCMS (ES) m/z = 515, 517 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.77 (dd, J=15.66, 9.09 Hz, 1 H) 8.02 (br. s., 3 H) 7.80 (s, 1 H) 7.66 - 7.72 (m, 2 H) 7.54 - 7.61 (m, 2 H) 7.41 - 7.48 (m, 1 H) 4.42 - 4.47 (m, 1 H) 3.71 (s, 3 H) 2.98 - 3.06 (m, 4 H) 2.66 (dd, J=7.45, 3.16 Hz, 2 H) 1.15 (t, J=7.45 Hz, 3 H).

Example 102



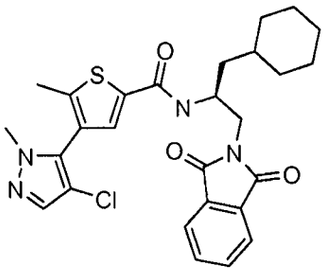
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



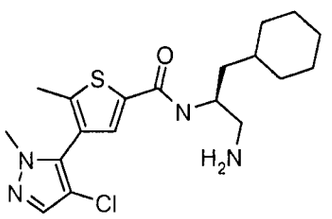
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.75 g, 11.64 mmol)[Prepared in Example 99] and N-chlorosuccinimide (1.55 g, 11.64 mmol) in tetrahydrofuran (58 ml) was stirred in a sealed tube for 1h at 70 °C. Sodium hydroxide (9.70 ml, 58 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 20% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (2.3 g, 8.96 mmol, 77 % yield) as a yellow oil: LCMS (ES) m/e 257, 259 (M, M+2)+.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (159 mg, 0.62 mmol), N,N-diisopropylethylamine (0.54 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.62 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 45% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (231 mg, 0.44 mmol, 71 % yield) as a clear oil: LCMS (ES) m/e 525, 527 $(M, M+2)^+$.

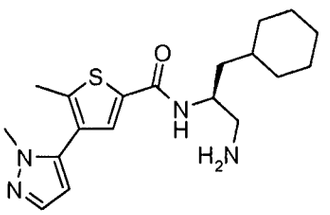
c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (231 mg, 0.44 mmol) in tetrahydrofuran (2.20 ml) and methanol (2.20 ml) at 25 °C was added hydrazine (0.14 ml, 4.40 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by

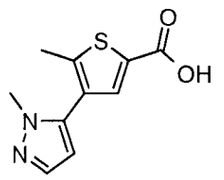
column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then transferred to the HCl salt adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (124 mg, 0.27 mmol, 60 % yield) as a yellow solid: LCMS (ES) m/z = 394, 396 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.51 (br. s., 1 H) 7.97 (br. s., 3 H) 7.86 (s, 1 H) 7.70 (s, 1 H) 4.24 - 4.26 (m, 1 H) 3.71 (s, 3 H) 2.90 - 2.99 (m, 2 H) 2.36 (s, 3 H) 1.75 - 1.79 (m, 1 H) 1.61 1.64 (m, 4 H) 1.48 - 1.51 (m, 1 H) 1.31 - 1.36 (m, 2 H) 1.10 - 1.14 (m, 2 H) 0.91 - 0.94 (m, 2 H).

Example 103



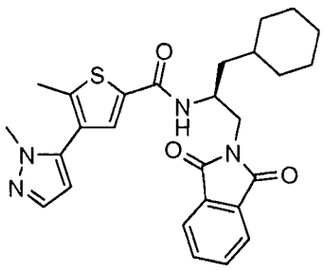
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



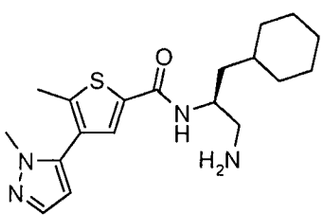
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 1.06 mmol)[Prepared in Example 99] in 6N sodium hydroxide (1.76 ml, 10.6 mmol) and tetrahydrofuran (5.290 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (151 mg, 0.68 mmol, 64 % yield) as a white solid; LCMS (ES) m/z = 223 $(M+H)^+$.

b) N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (138 mg, 0.62 mmol), N,N-diisopropylethylamine (0.541 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.62 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (285 mg, 0.581 mmol, 94 % yield) as a white foam: LCMS (ES) m/e 491, 493 (M, M+2)$^+$.

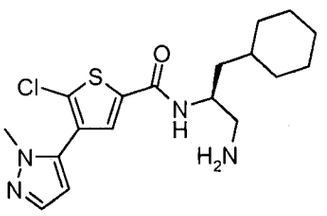
c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (285 mg, 0.581 mmol) in tetrahydrofuran (2.905 ml) and methanol (2.91 ml) at 25 °C was added hydrazine (0.18 ml, 5.81 mmol) dropwise. After 12h, the solution was

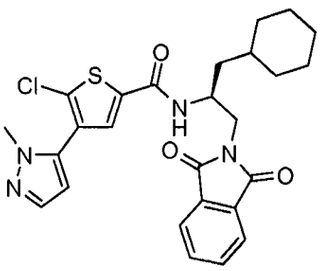
concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then transferred to the HCl salt by adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (173 mg, 0.40 mmol, 69 % yield) as a yellow solid: LCMS (ES) m/z = 360 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.55 (d, *J*=8.59 Hz, 1 H) 8.01 (br. s., 3) 7.94 (s, 1 H) 7.52 (d, *J*=2.02 Hz, 1 H) 6.35 (d, *J*=1.77 Hz, 1 H) 4.24 - 4.27 (m, 1 H) 3.77 (s, 3 H) 2.91 - 2.94 (m, 2 H) 2.39 (s, 3 H) 1.72 - 1.77 (m, 1 H) 1.60 - 1.64 (m, 4 H) 1.49 - 1.52 (m, 1 H) 1.21 - 1.29 (m, 2 H) 1.15 - 1.25 (m, 2 H) 0.89 - 0.94 (m, 2 H).

Example 104



Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

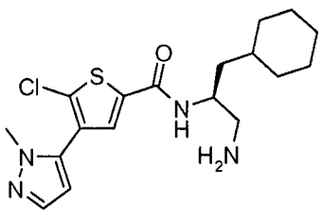
a) 5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (150 mg, 0.62 mmol)[Prepared in Example 95], N,N-diisopropylethylamine (0.54 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.62 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-

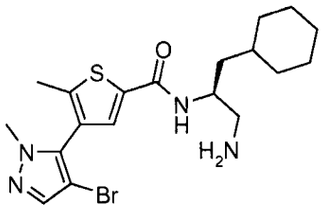
phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 45% EtOAc in hexanes) yielding 5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (168 mg, 0.33 mmol, 53 % yield) as a clear oil: LCMS (ES) m/e 511, 513 (M, M+2)$^+$.

b) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



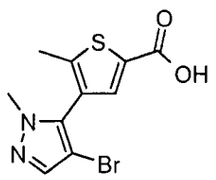
To a solution of 5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (168 mg, 0.33 mmol) in tetrahydrofuran (1.644 ml) and methanol (1.644 ml) at 25 °C was added hydrazine (0.10 ml, 3.29 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (silica, 5% MeOH in DCM (1% NH_4OH)). The free base was then transferred to the HCl salt adding excess 4M HCl in dioxane (1 mL) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (79 mg, 0.17 mmol, 53 % yield) as a yellow solid: LCMS (ES) m/z = 380, 382 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 8.82 (d, *J*=8.59 Hz, 1 H) 8.10 (s, 1 H) 7.99 (br. s., 3 H) 7.55 (d, *J*=1.77 Hz, 1 H) 6.48 (d, *J*=2.02 Hz, 1 H) 4.22 - 4.28 (m, 1 H) 3.81 (s, 3 H) 2.90 - 2.95 (m, 2 H) 1.74 - 1.78 (m, 1 H) 1.62 - 1.65 (m, 4 H) 1.48-1.51 (m, 1 H) 1.37 - 1.39 (m, 2 H) 1.09 - 1.13 (m, 2 H) 0.92 - 0.96 (m, 2 H).

Example 105



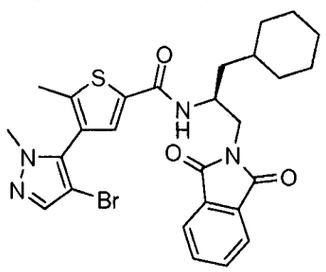
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 1.058 mmol)[prepared in Example 99] and N-bromosuccinimide (188 mg, 1.06 mmol) in tetrahydrofuran (5.29 ml) was stirred in a sealed tube for 1h at 70 °C. Sodium hydroxide (3.53 ml, 21.16 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (289 mg, 0.96 mmol, 91 % yield) as a yellow oil: LCMS (ES) m/e 301, 303 $(M, M+2)^+$.

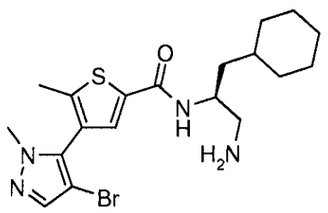
b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (187 mg, 0.62 mmol), N,N-diisopropylethylamine (0.54 ml, 3.10 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione

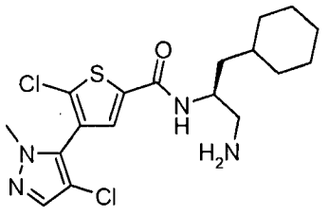
(200 mg, 0.62 mmol))[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (347 mg, 0.74 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 50% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (226 mg, 0.40 mmol, 64 % yield) as a white foam: LCMS (ES) m/e 569, 571 (M, M+2)$^+$.

c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



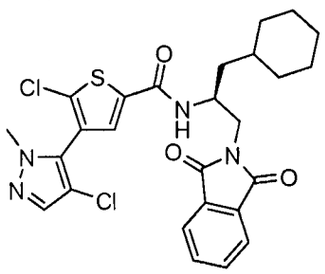
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (226 mg, 0.40 mmol) in tetrahydrofuran (1.98 ml) and methanol (1.98 ml) at 25 °C was added hydrazine (0.13 ml, 3.97 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography. The free base was then transferred to the HCl salt adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (153 mg, 0.30 mmol, 75 % yield) as a yellow solid: LCMS (ES) m/z =439, 441 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.51 (br. s., 1 H) 7.96 (br. s., 3 H) 7.83 (br. s., 1 H) 7.70 (s, 1 H) 4.21 - 4.25 (m, 1 H) 3.94 (s, 3H) 2.89 - 2.92 (m, 2 H) 2.35 (s, 3 H) 1.76 - 1.79 (m, 1 H) 1.60 - 1.64 (m, 4 H) 1.48 - 1.54 (m, 1 H) 1.26 - 1.32 (m, 2 H) 1.09 - 1.16 (m, 2 H) 0.92 - 0.95 (m, 1 H) 0.82 - 0.86 (m, 1 H).

Example 106



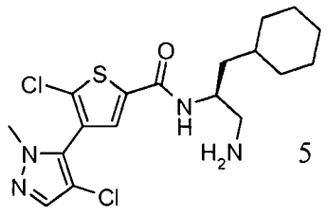
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (216 mg, 0.78 mmol)[prepared according to Example 96], N,N-diisopropylethylamine (0.68 ml, 3.90 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (252 mg, 0.78 mmol)[Prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (401 mg, 0.86 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40% EtOAc in hexanes) yielding 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (303 mg, 0.55 mmol, 71 % yield) as a clear oil: LCMS (ES) m/e 545, 547 (M, M+2)$^+$.

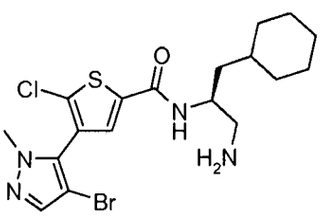
b) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



5

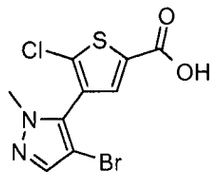
To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (303 mg, 0.55 mmol) in tetrahydrofuran (2.78 ml) and methanol (2.78 ml) at 25 °C was added hydrazine (0.17 ml, 5.55 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then converted to the HCl salt by adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (190 mg, 0.389 mmol, 70.0 % yield) as a yellow solid: LCMS (ES) m/z =415, 417 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (br. s., 1 H) 8.06 (s, 4 H) 7.74 (s, 1 H) 4.25 (dd, *J*=8.84, 4.29 Hz, 1 H) 3.77 (s, 3 H) 2.87 - 2.93 (m, 2 H) 1.71 - 1.79 (m, 1H) 1.64 (d, *J*=9.85 Hz, 3 H) 1.54 (br. s., 1 H) 1.48 (br. s., 1 H) 1.37 (dd, *J*=13.26, 4.93 Hz, 1 H) 1.14 (br. s., 1 H) 1.17 (d, *J*=7.33 Hz, 2 H) 0.93 (d, *J*=10.86 Hz, 1 H) 0.82 - 0.89 (m, 1 H).

Example 107



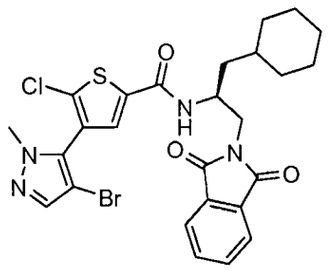
Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid



A solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (50 mg, 0.21 mmol)[prepared in Example 95] and NBS (36.7 mg, 0.21 mmol) in tetrahydrofuran (2.06 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (82 mg, 0.16 mmol, 79 % yield) as a yellow oil: LCMS (ES) m/e 257, 259 (M, M+2)$^+$.

b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (81 mg, 0.252 mmol), n,n-diisopropylethylamine (0.22 ml; 1.26 mmol) and 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (81 mg, 0.25 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (141 mg, 0.302 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (47 mg, 0.080 mmol, 31.6 % yield) as a clear oil: LCMS (ES) m/e 589, 591 (M, M+2)$^+$.

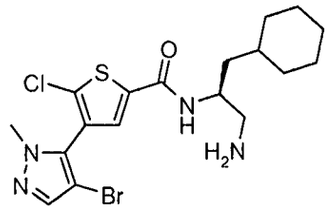
c) N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

Organización y
Digitalización CSA Ltda

PATENTE DE INVENCIÓN

09-82387

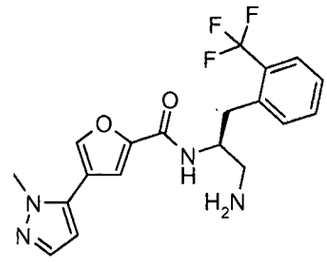
2/5



82387/07
T 2

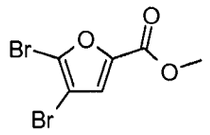
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (48 mg, 0.08 mmol) in tetrahydrofuran (0.41 ml) and methanol (0.41 ml) at 25 °C was added hydrazine (0.03 ml, 0.81 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was then converted to the HCl salt by adding excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide (11 mg, 0.02 mmol, 24 % yield) as a yellow solid: LCMS (ES) m/z =459, 461 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 (br. s., 1 H) 7.96 (br. s., 4 H) 7.74 (s, 1 H) 4.21 - 4.26 (m, 1 H) 3.77 (s, 3 H) 2.92 - 2.99 (m, 2 H) 1.73 - 1.79 (m, 1 H) 1.62 - 1.67 (m, 4 H) 1.49 - 1.51 (m, 1 H) 1.25 (br. s., 2 H) 1.06 - 1.13 (m, 2 H) 0.95 (d, *J*=6.82 Hz, 1 H) 0.82 - 0.89 (m, 1 H).

Example 108



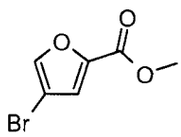
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4,5-dibromo-2-furancarboxylate



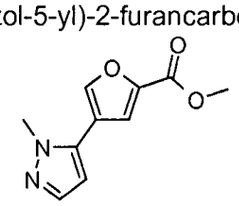
To a solution of 4,5-dibromo-2-furancarboxylic acid (5.7 g, 21.1 mmol) in methanol (106 ml) was added sulfuric acid (11.3 ml, 211 mmol). The resulting solution stirred at 50 °C over 4days. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4,5-dibromo-2-furancarboxylate (5.5 g, 19.4 mmol, 92 % yield): LCMS (ES) m/e 283 $(M+H)^+$.

b) methyl 4-bromo-2-furancarboxylate



To a solution of methyl 4,5-dibromo-2-furancarboxylate (1 g, 3.52 mmol) in tetrahydrofuran (14.1 ml) at -40 °C was added isopropylmagnesium chloride (1.85 ml, 3.70 mmol). After 2h, H_2O (3.52 ml) was added and the solution warmed to 25 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (3% EtOAc in hexanes) affording methyl 4-bromo-2-furancarboxylate (470 mg, 2.04 mmol, 58 % yield) as a white solid: LCMS (ES) m/e 204, 206 (M, M+2)$^+$.

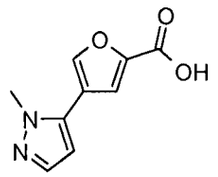
c) methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



A solution of methyl 4-bromo-2-furancarboxylate (470 mg, 2.29 mmol), potassium carbonate (1.58 g, 11.46 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (525 mg, 2.52 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (58.6 mg, 0.115 mmol) in 1,4-Dioxane (9.5 ml) and water (1.9 ml) was stirred at 80 °C in a sealed tube for 1h. The solution was partitioned between H_2O-DCM and the aqueous phase was

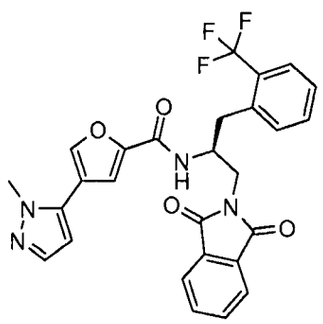
washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (30% EtOAc in hexanes) affording methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (124 mg, 0.60 mmol, 26 % yield) as a white powder: LCMS (ES) m/e 206 $(M+H)^+$.

d) 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (124 mg, 0.60 mmol) in 6N sodium hydroxide (2.0 ml, 12.0 mmol) and tetrahydrofuran (3.0 ml) was stirred at 70 °C in a sealed tube for 2h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (54 mg, 0.28 mmol, 47 % yield) as a white solid: LCMS (ES) m/e 192 $(M+H)^+$.

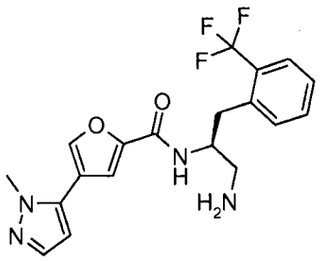
e) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



To a solution of 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (54 mg, 0.28 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (108 mg, 0.28 mmol)[prepared in Preparation 6] and N,N-diisopropylethylamine (0.24 ml, 1.40 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (158 mg, 0.34 mmol) in one portion.

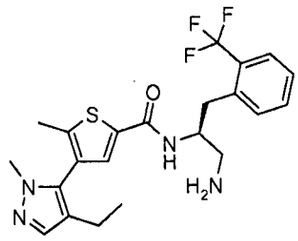
The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purfied via column chromatography (silica, 50% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (100 mg, 0.14 mmol, 50 % yield) as a white solid: LCMS (ES) m/e 523 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



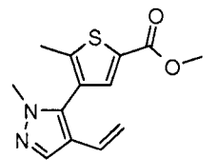
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (100 mg, 0.19 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) at 25 °C was added hydrazine (0.06 ml, 1.91 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (56 mg, 0.12 mmol, 62 % yield) as a yellow solid: LCMS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (d, *J*=9.09 Hz, 1 H) 8.28 (s, 1 H) 8.07 (br. s., 3 H) 7.69 (d, *J*=8.08 Hz, 1 H) 7.56 (d, *J*=8.08 Hz, 2 H) 7.50 (s, 1 H) 7.45 (d, *J*=1.77 Hz, 2 H) 6.51 (d, *J*=1.77 Hz, 1 H) 4.50 - 4.57 (m, 1 H) 3.93 (s, 3 H) 3.02 - 3.16 (m, 4 H).

Example 109



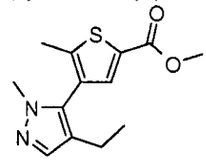
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (200 mg, 0.64 mmol)[prepared in Example 99], potassium carbonate (438 mg, 3.17 mmol), bis(tri-t-butylphosphine)palladium(0) (324 mg, 0.64 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (77 mg, 0.32 mmol) in 1,4-dioxane (5.3 ml) and H_2O (1 ml) was stirred at 80 °C in a sealed tube for 12h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (135 mg, 0.515 mmol, 81 % yield) as a yellow oil: LCMS (ES) m/z = 250 $(M+H)^+$.

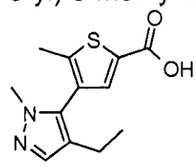
b) methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



To a solution of methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (135 mg, 0.52 mmol) in methanol (2.6 ml) was added Pd-C (21.9 mg, 0.21 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-

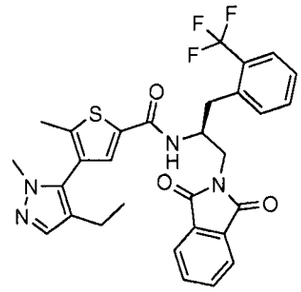
thiophenecarboxylate (145 mg, 0.51 mmol, 99 % yield) as a yellow oil which was used without further purification: LCMS (ES) m/e 265 $(M+H)^+$.

c) 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



A solution of methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (145 mg, 0.55 mmol) in 6N sodium hydroxide (1.8 ml, 10.97 mmol) and tetrahydrofuran (4.8 ml) was stirred at 60 °C in a sealed tube for 12h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (137 mg, 0.55 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 250 $(M+H)^+$.

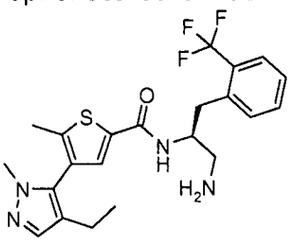
d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



To a solution of 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (137 mg, 0.55 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (211 mg, 0.55 mmol)[prepared in Preparation 6] and diisopropylethylamine (0.48 ml, 2.74 mmol) in Dichloromethane (5.47 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (281 mg, 0.60 mmol) in one portion. The solution stirred at 25 °C for 1h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 40-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-

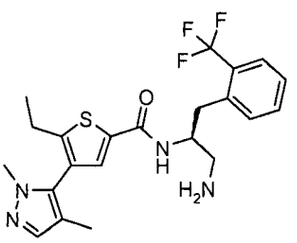
1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (262 mg, 0.45 mmol, 82 % yield) as a clear oil: LCMS (ES) m/e 581 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



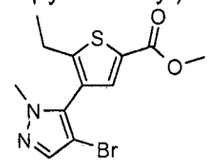
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (262 mg, 0.45 mmol) in tetrahydrofuran (2.256 ml) and methanol (2.256 ml) at 25 °C was added hydrazine (0.14 ml, 4.51 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (170 mg, 0.32 mmol, 72 % yield) as a yellow solid: LCMS (ES) m/z = 451 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.72 (br. s., 1 H) 8.05 (br. s., 2 H) 7.76 (s, 1 H) 7.69 (d, *J*=7.83 Hz, 1 H) 7.49 - 7.52 (m, 2 H) 7.40 - 7.45 (m, 2 H) 4.42 - 4.47 (m, 1 H) 3.61 (br. s., 3 H) 3.01 - 3.07 (m, 4 H) 2.52 - 2.59 (m, 2 H) 2.26 (s, 3 H) 1.02 - 1.09 (m, 3 H).

Example 110



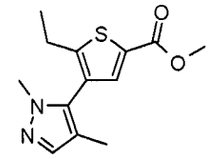
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



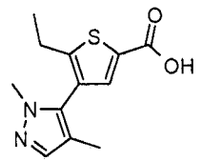
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (980 mg, 3.92 mmol)[prepared in Example 98] and N-bromosuccinimide (697 mg, 3.92 mmol) in tetrahydrofuran (19.6 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated then purified via column chromatography (silica, 10-40% EtOAC in hexanes) yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (1.1 g, 3.34 mmol, 85 % yield) as a yellow oil: LCMS (ES) m/e 329, 331 $(M, M+2)^+$.

b) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



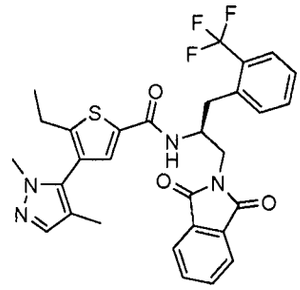
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (300 mg, 0.911 mmol), potassium carbonate (630 mg, 4.56 mmol), $PdCl_2$(dppf) (66.7 mg, 0.091 mmol) and trimethylboroxin (0.25 ml, 1.82 mmol) in N,N-dimethylformamide (9.1 ml) was stirred at 110 °C in a sealed tube for 2h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (143 mg, 0.51 mmol, 56 % yield) as a yellow oil: LCMS (ES) m/z = 265 $(M+H)^+$.

c) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



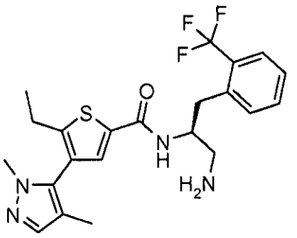
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (143 mg, 0.54 mmol) in 6N sodium hydroxide (0.90 ml, 5.41 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (136 mg, 0.54 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 251 $(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide



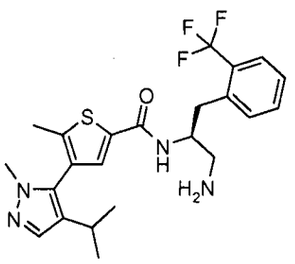
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (130 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.57 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (278 mg, 0.43 mmol, 82 % yield) as a yellow oil: LCMS (ES) m/e 581 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide



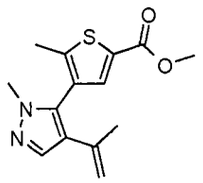
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-thiophenecarboxamide (278 mg, 0.48 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.15 ml, 4.79 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (3-15% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 2M HCl in Et_2O (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide (196 mg, 0.36 mmol, 76 % yield) as a yellow solid: LCMS (ES) m/z = 451 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.86 - 8.93 (m, 1 H) 8.15 (br. s., 3 H) 7.83 (s, 1 H) 7.69 (d, *J*=7.58 Hz, 1 H) 7.55 (br. s., 1 H) 7.52 (t, *J*=7.45 Hz, 1 H) 7.42 (t, *J*=7.45 Hz, 1 H) 7.38 (s, 1 H) 4.22 - 4.27 (m,1 H) 3.62 (s, 3 H) 2.97 - 3.09 (m, 4 H) 2.60 (q, *J*=7.49 Hz, 2 H) 1.88 (s, 3 H) 1.13 (t, *J*=7.58 Hz, 3 H).

Example 111



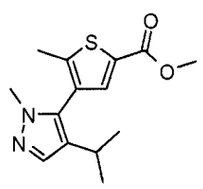
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide

a) methyl 5-methyl-4-[1-methyl-4-(1-methylethenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate



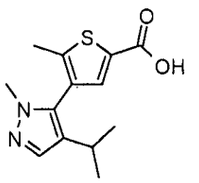
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (300 mg, 0.95 mmol), potassium carbonate (658 mg, 4.76 mmol), bis(tri-t-butylphosphine)palladium(0) (24.32 mg, 0.05 mmol) and 4,4,5,5-tetramethyl-2-(1-methylethenyl)-1,3,2-dioxaborolane (0.18 ml, 0.95 mmol) in 1,4-dioxane (5.3 ml) and H_2O (1.0 ml) was stirred at 80 °C in a sealed tube for 12h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-methyl-4-[1-methyl-4-(1-methylethenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (171 mg, 0.58 mmol, 61 % yield) as a yellow oil: LCMS (ES) m/z = 276 $(M+H)^+$.

b) methyl 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate



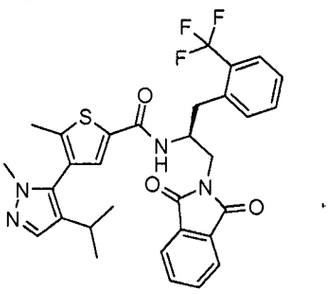
To a solution of methyl 5-methyl-4-[1-methyl-4-(1-methylethenyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (171 mg, 0.62 mmol) in methanol (3 ml) was added $PdOH_2$ (34.8 mg, 0.25 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (173 mg, 0.62 mmol, 100 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

c) 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylic acid



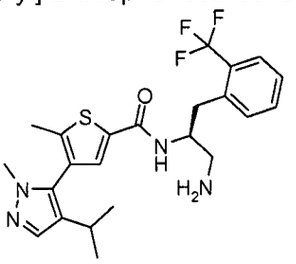
A solution of methyl 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylate (173 mg, 0.62 mmol) in 6N sodium hydroxide (1 ml, 6.21 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylic acid (148 mg, 0.49 mmol, 79 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide



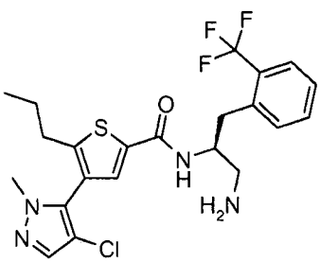
To a solution of 5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxylic acid (137 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[Prepared in Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.572 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide (211 mg, 0.334 mmol, 64.2 % yield) as a yellow oil: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide



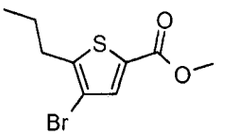
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide (211 mg, 0.36 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.11 ml, 3.55 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide (108 mg, 0.20 mmol, 57 % yield) as a yellow solid: LCMS (ES) m/z = 465 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (d, *J*=8.59 Hz, 1 H) 8.07 (br. s., 3 H) 7.74 (s, 1 H) 7.65 - 7.68 (m, 1 H) 7.55 - 7.60 (m, 1 H) 7.46 - 7.49 (m, 1 H) 7.39 - 7.46 (m, 2 H) 4.47 (br. s., 1 H) 3.57 (s, 3 H) 2.99 - 3.05 (m, 4 H) 2.49 - 2.52 (m, 1 H) 2.25 (s, 3 H) 1.07 - 1.14 (m, 6 H).

Example 112



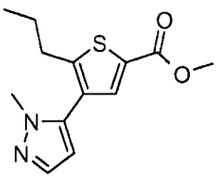
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide

a) methyl 4-bromo-5-propyl-2-thiophenecarboxylate



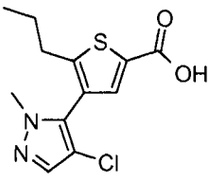
To a solution of 4-bromo-5-propyl-2-thiophenecarboxylic acid (5.0 g, 20.07 mmol) in methanol (100 ml) was added sulfuric acid (5.35 ml, 100 mmol). The resulting solution stirred at 50 °C for 36h. H_2O (50 mL) was added the aqueous phase was washed several times with DCM. The combined organic fractions were washed with saturated $NaHCO_3$, dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4-bromo-5-propyl-2-thiophenecarboxylate (5.1 g, 18.61 mmol, 93 % yield) as a yellow oil: LCMS (ES) m/e 262, 264 $(M, M+2)^+$.

b) methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate



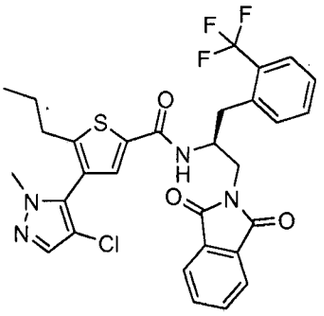
A solution of methyl 4-bromo-5-propyl-2-thiophenecarboxylate (1.0 g, 3.80 mmol), potassium carbonate (2.63 g, 19.00 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.949 g, 4.56 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.097 g, 0.19 mmol) were combined in a sealed tube and stirred at 80 °C for 1h. The reaction contents were then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated and purified by column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (1.07 g, 3.76 mmol, 99 % yield) as a yellow oil: LCMS (ES) m/e 265 $(M+H)^+$.

c) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid



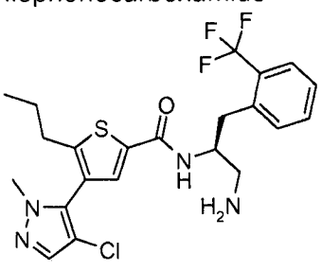
A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (356 mg, 1.35 mmol) and N-chlorosuccinimide (180 mg, 1.35 mmol) in tetrahydrofuran (6.7 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (2.2 ml, 13.47 mmol) was added in one portion and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (357 mg, 1.25 mmol, 93 % yield) as a yellow oil: LCMS (ES) m/e 271, 273 (M, M+2)$^+$.

d) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide



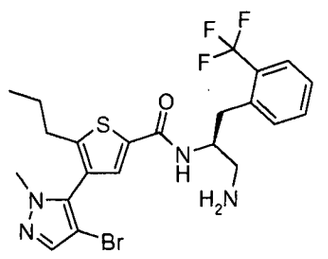
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (148 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[Prepared according to Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.57 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (245 mg, 0.39 mmol, 75 % yield) as a yellow oil: LCMS (ES) m/e 615, 617 (M, M+2)$^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide



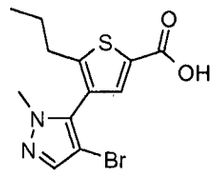
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (245 mg, 0.40 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.12 ml, 3.98 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide (178 mg, 0.32 mmol, 80 % yield) as a yellow solid: LCMS (ES) m/z = 485, 487 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.96 (br. s., 1 H) 8.13 (br. s., 3 H) 7.93 (s, 1 H) 7.66 - 7.73 (m, 2 H) 7.62 (br. s., 1 H) 7.55 (t, *J*=7.45 Hz, 1 H) 7.42 (t, *J*=7.45 Hz, 1 H) 4.48 (br. s., 1 H) 3.71 (s, 3 H) 2.99 - 3.08 (m, 4 H) 2.63 (t, *J*=7.20 Hz, 2 H) 1.53 - 1.57 (m, 2 H) 0.83 (t, *J*=7.33 Hz, 3 H).

Example 113



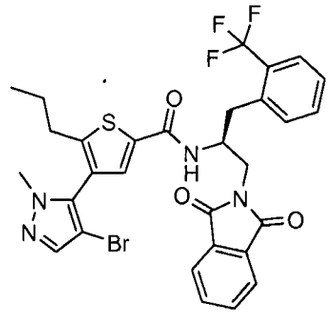
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (714 mg, 2.70 mmol)[prepared in Example 112] and N-bromosuccinimide (481 mg, 2.70 mmol) in tetrahydrofuran (12 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half of the solution was treated with 6N sodium hydroxide (2.251 ml, 13.51 mmol). The reaction mixture stirred at 70 °C in a sealed tube for 12h and was partitioned between H_2O-DCM. The pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly affording 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (445 mg, 1.35 mmol, 50 % yield): LCMS (ES) m/e 329, 331 $(M, M+2)^+$.

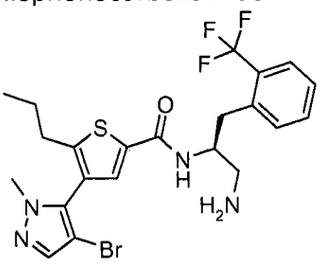
b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide



To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (171 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.45 ml, 2.60 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (267 mg, 0.57 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-

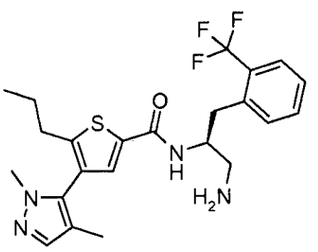
(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (251 mg, 0.37 mmol, 72 % yield) as a yellow oil: LCMS (ES) m/e 659,661 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide



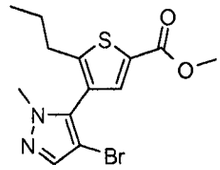
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (251 mg, 0.38 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.12 ml, 3.81 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide (178 mg, 0.30 mmol, 78 % yield) as a yellow solid: LCMS (ES) m/z = 529, 531 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.94 (d, *J*=8.84 Hz, 1 H) 8.10 (br. s., 3 H) 7.87 (d, *J*=1.77 Hz, 1 H) 7.65 - 7.72 (m, 2 H) 7.58 (dd, *J*=14.78, 7.71 Hz, 2 H) 7.43 (t, *J*=7.45 Hz, 1 H) 4.48 (br. s., 1 H) 3.71 (s, 3 H) 2.99 - 3.08 (m, 4 H) 2.58 - 2.66 (m, 2 H) 1.53 (ddd, *J*=13.89, 6.82, 6.57 Hz, 2 H) 0.83 (dd, *J*=7.33, 2.02 Hz, 3 H).

Example 114



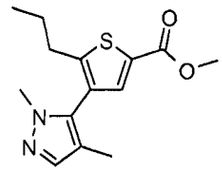
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate



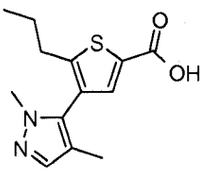
A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (714 mg, 2.70 mmol) and N-bromosuccinimide (481 mg, 2.70 mmol) in tetrahydrofuran (12 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and used directly yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (464 mg, 1.35 mmol, 50 % yield) as an orange oil: LCMS (ES) m/e 343, 345 (M, M+2)$^+$.

b) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propylthiophene-2-carboxylate



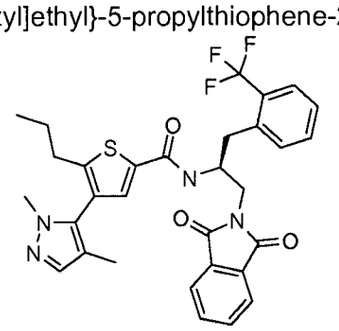
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (242 mg, 0.71 mmol), $PdCl_2$(dppf) (52 mg, 0.07 mmol), potassium carbonate (487 mg, 3.53 mmol) and trimethylboroxine (0.20 ml, 1.41 mmol) in N,N-Dimethylformamide (3.5 ml) was stirred at 110 °C in a sealed tube for 2h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (184 mg, 0.60 mmol, 84 % yield) as a yellow oil: LCMS (ES) m/z = 279 (M+H)$^+$.

c) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propylthiophene-2-carboxylic acid



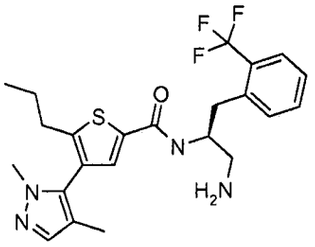
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylate (0.184 g, 0.66 mmol) in 6N sodium hydroxide (2.2 ml, 13.22 mmol) and tetrahydrofuran (6.6 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (180 mg, 0.66 mmol, 100 % yield) as a yellow oil: LCMS (ES) m/e 265 $(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[2-(trifluoromethyl)benzyl]ethyl}-5-propylthiophene-2-carboxamide



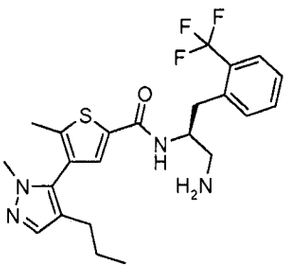
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxylic acid (180 mg, 0.68 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (262 mg, 0.68 mmol)[prepared in Preparation 6] and diisopropylethylamine (0.59 ml, 3.40 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (350 mg, 0.75 mmol) in one portion. The solution stirred at 25 °C for 2h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (243 mg, 0.41 mmol, 60 % yield) as a yellow oil: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-{(1S)-2-amino-1-[2-(trifluoromethyl)benzyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propylthiophene-2-carboxamide



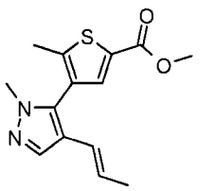
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-propyl-2-thiophenecarboxamide (243 mg, 0.41 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) at 25 °C was added hydrazine (0.13 ml, 4.09 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide (172 mg, 0.30 mmol, 74 % yield) as a yellow solid: LCMS (ES) m/z = 465 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (br. s., 1 H) 8.08 (br. s., 3 H) 7.78 (s, 1 H) 7.69 (d, *J*=7.58 Hz, 1 H) 7.50 - 7.55 (m, 2 H) 7.43 (t, *J*=7.71 Hz, 1 H) 7.37 (s, 1 H) 4.49 (d, *J*=10.36 Hz, 1 H) 3.61 (s, 3 H) 2.99 - 3.06 (m, 4 H) 2.54 - 2.59 (m, 2 H) 1.87 (s, 3 H) 1.48 - 1.55 (m, 2 H) 0.81 (t, *J*=7.33 Hz, 3 H).

Example 115



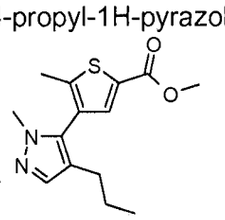
Preparation of N-{(1S)-2-amino-1-[2-(trifluoromethyl)benzyl]ethyl}-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)thiophene-2-carboxamide

a) methyl 5-methyl-4-{1-methyl-4-[(1E)-prop-1-en-1-yl]-1H-pyrazol-5-yl}thiophene-2-carboxylate



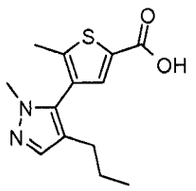
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (320 mg, 1.015 mmol)[prepared in Example 99], potassium carbonate (702 mg, 5.08 mmol), bis(tri-t-butylphosphine)palladium(0) (25.9 mg, 0.05 mmol) and(1Z)-1-propen-1-ylboronic acid (87 mg, 1.01 mmol) in 1,4-dioxane (5.3 ml) and water (1.3 ml) was stirred at 80 °C in a sealed tube for 12h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-methyl-4-{1-methyl-4-[(1Z)-1-propen-1-yl]-1H-pyrazol-5-yl}-2-thiophenecarboxylate (243 mg, 0.88 mmol, 87 % yield) as a yellow oil: LCMS (ES) m/z = 277 $(M+H)^+$.

b) methyl 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



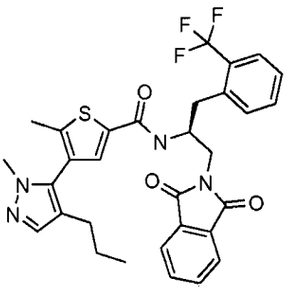
To a solution of methyl 5-methyl-4-{1-methyl-4-[(1Z)-1-propen-1-yl]-1H-pyrazol-5-yl}-2-thiophenecarboxylate (243 mg, 0.88 mmol) in methanol (6.8 ml) was added $Pd(OH)_2$ (49 mg, 0.35 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (217 mg, 0.69 mmol, 78 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

c) 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



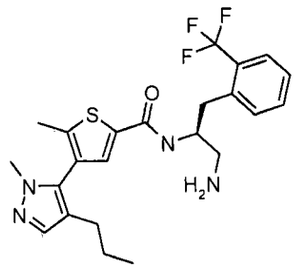
A solution of methyl 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (217 mg, 0.78 mmol) in 6N sodium hydroxide (2.60 ml, 15.59 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (242 mg, 0.78 mmol, 100 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



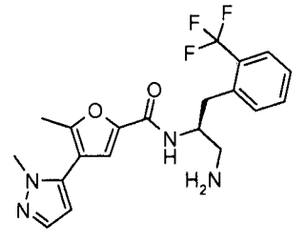
To a solution of 5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (206 mg, 0.78 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (300 mg, 0.78 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.68 ml, 3.90 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (400 mg, 0.86 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (283 mg, 0.46 mmol, 60 % yield) as a yellow oil: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



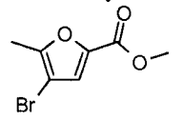
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (283 mg, 0.48 mmol) in tetrahydrofuran (2.4 ml) and methanol (2.4 ml) at 25 °C was added hydrazine (0.15 ml, 4.76 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (186 mg, 0.35 mmol, 73 % yield) as a yellow solid: LCMS (ES) m/z = 465 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (br. s., 1 H) 8.13 (br. s., 3 H) 7.79 (s, 1 H) 7.68 (d, *J*=7.58 Hz, 1 H) 7.59 (d, *J*=7.07 Hz, 1 H) 7.42 - 7.51 (m, 1 H) 7.38 - 7.45 (m, 2 H) 4.47 (br. s., 1 H) 3.61 (d, *J*=2.78 Hz, 3 H) 2.99 - 3.08 (m, 4 H) 2.25 (s, 3 H) 2.11 - 2.21 (m, 2 H) 1.41 - 1.48 (m, 2 H) 0.83 (br. s., 3 H).

Example 116



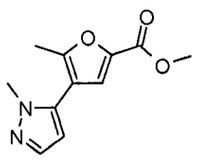
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4-bromo-5-methyl-2-furancarboxylate



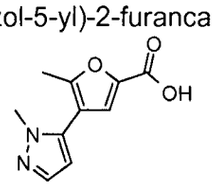
To a solution of methyl 5-methyl-2-furancarboxylate (1.5 g, 10.70 mmol) and aluminum trichloride (2.14 g, 16.06 mmol) in chloroform (21 ml) at 0 °C was added bromine (0.77 ml, 14.99 mmol). The resulting solution stirred at 0 °C and warmed to RT over 12h. This reaction was run in batches (1.5g and 1g) and the batches were combined, added to ice and partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (0.5-10% EtOAc in hexanes) affording the title compound (2.1 g, 54%) as a white solid; LCMS (ES) m/z = 219, 221 $(M, M+2)^+$.

b) methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



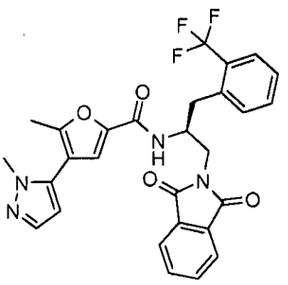
A solution of methyl 4-bromo-5-methyl-2-furancarboxylate (2.1 g, 9.59 mmol), potassium carbonate (6.63 g, 47.9 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.19 g, 10.55 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.24 g, 0.48 mmol) in 1,4-dioxane (40 ml) and water (8 ml) was stirred at 80 °C in a sealed tube for 1h. 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.19 g, 10.55 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.245 g, 0.48 mmol) were added and the reaction stirred an additional 1h and was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-40% EtOAc in hexanes) affording methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (1.7 g, 7.72 mmol, 81 % yield) as a yellow oil: LCMS (ES) m/e 221 $(M+H)^+$.

c) 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



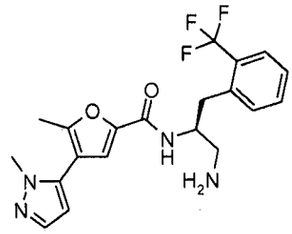
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (200 mg, 0.91 mmol) in 6N sodium hydroxide (2.3 ml, 13.62 mmol) and tetrahydrofuran (4.5 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (130 mg, 0.57 mmol, 63 % yield) as a yellow oil: LCMS (ES) m/e 207 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



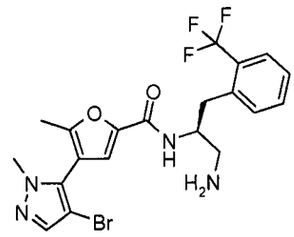
To a solution of 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (130 mg, 0.63 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (243 mg, 0.63 mmol)[prepared in Preparation 6] and diisopropylethylamine (0.55 ml, 3.15 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (324 mg, 0.69 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (190 mg, 0.23 mmol, 37 % yield) as a clear oil: LCMS (ES) m/e 537 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



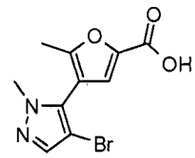
To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (190 mg, 0.35 mmol) in tetrahydrofuran (1.5 ml) and methanol (1.5 ml) at 25 °C was added hydrazine (0.11 ml, 3.54 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (71 mg, 0.15 mmol, 42 % yield) as a yellow solid: LCMS (ES) m/z 407 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=9.60 Hz, 1 H) 8.04 (br. s., 3 H) 7.70 (d, *J*=7.83 Hz, 1 H) 7.53 - 7.59 (m, 2 H) 7.49 (d, *J*=1.77 Hz, 1 H) 7.38 - 7.45 (m, 2 H) 6.33 (br. s., 1 H) 4.52 (br. s., 1 H) 3.80 (s, 3 H) 2.98 - 3.09 (m, 4 H) 2.38 (s, 3 H).

Example 117



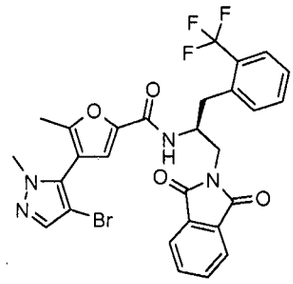
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



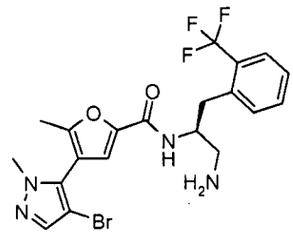
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (600 mg, 2.72 mmol)[prepared in Example 116] and n-bromosuccinimide (485 mg, 2.72 mmol) in tetrahydrofuran (13.6 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half of the solution was treated with 6N sodium hydroxide (4.54 ml, 27.2 mmol) which stirred at 70 °C in a sealed tube for 4h. The solution was partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly affording 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (369 mg, 1.29 mmol, 48 % yield) as an orange oil: LCMS (ES) m/e 285, 287 $(M, M+2)^+$.

b) 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



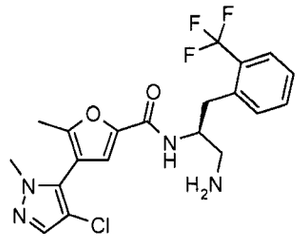
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (200 mg, 0.70 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (270 mg, 0.70 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.61 ml, 3.51 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (361 mg, 0.77 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (232 mg, 0.32 mmol, 46 % yield) as a clear oil: LCMS (ES) m/e 615, 617 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide



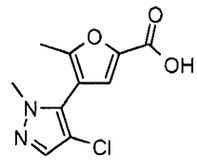
To a solution of 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (232 mg, 0.38 mmol) in tetrahydrofuran (2 ml) and methanol (2 ml) at 25 °C was added hydrazine (0.12 ml, 3.77 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide (106 mg, 0.19 mmol, 50 % yield) as a yellow solid: LCMS (ES) m/z = 485, 487 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=9.60 Hz, 1 H) 7.99 (br. s., 3 H) 7.68 (s, 2 H) 7.71 (d, *J*=8.08 Hz, 1 H) 7.59 (d, *J*=7.33 Hz, 1 H) 7.44 - 7.56 (m, 1 H) 7.25 - 7.33 (m, 1 H) 4.50 - 4.57 (m, 1 H) 3.74 (s, 3 H) 2.99 - 3.07 (m, 4 H) 2.32 (s, 3 H).

Example 118



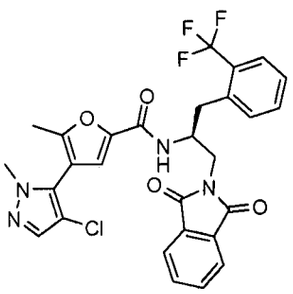
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



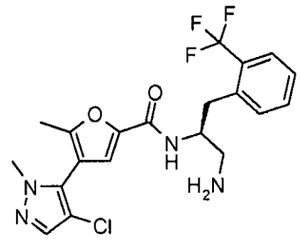
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.36 mmol) and N-chlorosuccinimide (182 mg, 1.36 mmol) in tetrahydrofuran (6.7 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (3.4 ml, 20.4 mmol) was added in one portion and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (275 mg, 1.14 mmol, 84 % yield) as a orange oil: LCMS (ES) m/e 241, 243 (M, M+2)$^+$.

b) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



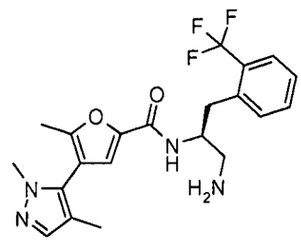
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (200 mg, 0.83 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (320 mg, 0.83 mmol)[prepared according to Preparation 6] and diisopropylethylamine (0.72 ml, 4.16 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (427 mg, 0.91 mmol) in one portion. The solution stirred at 25 °C for 12h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (246 mg, 0.40 mmol, 49 % yield) as a clear oil: LCMS (ES) m/e 571, 573 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide



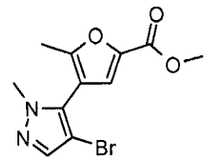
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (246 mg, 0.43 mmol) in tetrahydrofuran (2.1 ml) and methanol (2.1 ml) at 25 °C was added hydrazine (135 µl, 4.31 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide (125 mg, 0.24 mmol, 56 % yield) as a yellow solid: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (d, *J*=9.09 Hz, 1 H) 8.04 (br. s., 3 H) 7.65 - 7.72 (m, 2 H) 7.59 (d, *J*=7.33 Hz, 1 H) 7.57 (br. s., 1 H) 7.39 - 7.47 (m, 1 H) 7.29 - 7.37 (m, 1 H) 4.54 (br. s., 1 H) 3.73 (s, 3 H) 2.98 - 3.09 (m, 4 H) 2.33 (s, 3 H).

Example 119



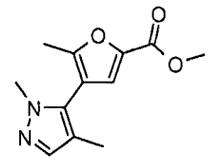
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate



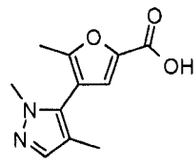
A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (600 mg, 2.72 mmol)[prepared in Example 116] and N-bromosuccinimide (485 mg, 2.72 mmol) in tetrahydrofuran (13 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was divided and half of the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (5-15% EtOAc in hexanes yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (130 mg, 0.41 mmol, 15 % yield) as an orange oil: LCMS (ES) m/e 299, 301 (M, M+2)$^+$.

b) methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate



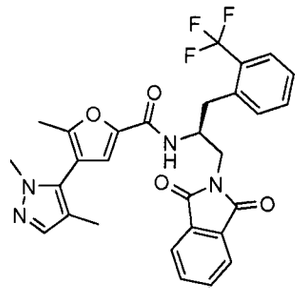
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (130 mg, 0.43 mmol) , potassium carbonate (300 mg, 2.17 mmol), $PdCl_2$(dppf) (15.9 mg, 0.02 mmol) and trimethylboroxine (0.12 ml, 0.87 mmol) in N,N-Dimethylformamide (3.5 ml) was stirred at 110 °C in a sealed tube for 2h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (60 mg, 0.26 mmol, 59 % yield) as a yellow oil: LCMS (ES) m/z = 235 (M+H)$^+$.

c) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



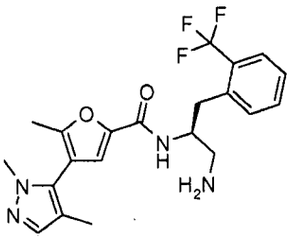
A solution of methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (60 mg, 0.26 mmol) in 6N sodium hydroxide (0.8 ml, 5.1 mmol) and tetrahydrofuran (2.5 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (53 mg, 0.24 mmol, 94 % yield) as a white foam: LCMS (ES) m/e 221$(M+H)^+$.

d) 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



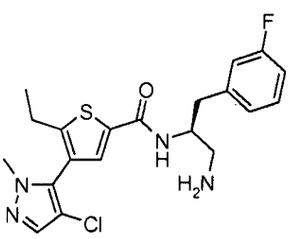
To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (53 mg, 0.24 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (93 mg, 0.24 mmol)[prepared according to Preparation 6] and N,N-diisopropylethylamine (0.21 ml, 1.20 mmol) in dichloromethane (2.4 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (124 mg, 0.26 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (113 mg, 0.21 mmol, 85 % yield) as a white foam: LCMS (ES) m/e 551 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide



To a solution of 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (113 mg, 0.21 mmol) in tetrahydrofuran (1 mL) and methanol (1 mL) at 25 °C was added hydrazine (64 µl, 2.05 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide (32 mg, 0.06 mmol, 32 % yield) as a yellow solid: LCMS (ES) m/z = 421 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.60 (d, *J*=9.09 Hz, 1 H) 8.05 (br. s., 3 H) 7.70 (d, *J*=7.58 Hz, 1 H) 7.54 - 7.61 (m, 2 H) 7.40 - 7.47 (m, 1 H) 7.35 (s, 1 H) 7.27 (s, 1 H) 4.54 (br. s., 1 H) 3.65 (s, 3 H) 2.98 - 3.07 (m, 4 H) 2.26 (s, 3 H) 1.90 (s, 3 H).

Example 120

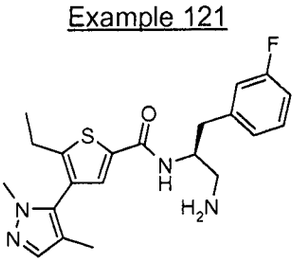


Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 100, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (155 mg, 0.46 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 421,

423 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (br. s., 1 H) 8.06 (br. s., 3 H) 7.85 (s, 1 H) 7.69 (s, 1 H) 7.28 - 7.36 (m, 1 H) 7.12 (d, *J*=7.07 Hz, 2 H) 7.03 (dd, *J*=17.05, 2.15 Hz, 1 H) 4.36 (br. s., 1 H) 3.69 (s, 3 H) 2.93 - 3.02 (m, 4 H) 2.67 (q, *J*=7.33 Hz, 2 H) 1.16 (t, *J*=7.45 Hz, 3 H).

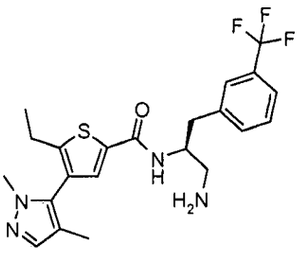
Example 121



N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 110, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (241 mg, 0.72 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 401 (M+H)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.76 (br. S., 1 H) 8.11 (br. S., 3 H) 7.79 (s, 1 H) 7.37 (s, 1 H) 7.28 – 7.36 (m, 1 H) 7.12 (d, *J*=6.82 Hz, 2 H) 7.03 (td, *J*=8.65, 1.64 Hz, 1 H) 4.41 – 4.43 (m, 1 H, obscured) 3.60 (br. S., 3 H) 2.99 – 3.02 (m, 4 H) 2.60 (q, *J*=7.33 Hz, 2 H) 1.86 (s, 3 H) 1.13 (t, *J*=7.45 Hz, 3 H).

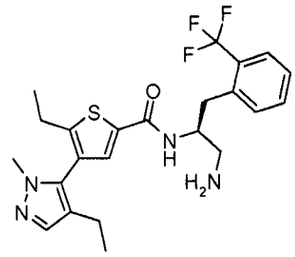
Example 122



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

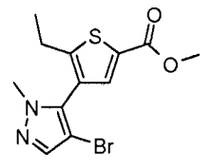
The title compound was prepared as a yellow solid according to Example 110, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (277 mg, 0.72 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 451 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.70 (br. s., 1 H) 8.06 (br. s., 3 H) 7.68 - 7.75 (m, 1 H) 7.52 (s, 1 H) 7.50 - 7.56 (m, 3 H) 7.37 (s, 1 H) 4.36 (d, *J*=8.84 Hz, 1 H) 3.58 (br. s., 3 H) 2.98 - 3.02 (m, 4 H) 2.55 - 2.61 (m, 2 H) 1.86 (s, 3 H) 1.12 (t, *J*=7.58 Hz, 3 H).

Example 123



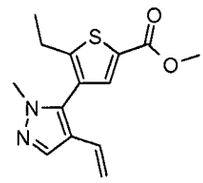
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



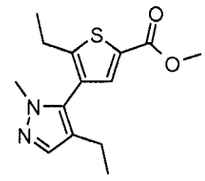
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1 g, 3.99 mmol)[prepared in Example 98] and N-bromosuccinimide (0.711 g, 3.99 mmol) in tetrahydrofuran (8 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (10-50% EtOAc in hexanes yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (1.2 g, 3.54 mmol, 89 % yield) as an orange oil: LCMS (ES) m/e 329, 331 (M, M+2)$^+$.

b) methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



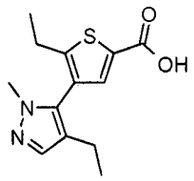
A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (300 mg, 0.911 mmol), potassium carbonate (630 mg, 4.56 mmol), bis(tri-t-butylphosphine)palladium(0) (23.29 mg, 0.05 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (110 mg, 0.45 mmol) in 1,4-dioxane (5 ml) and Water (1 ml) was stirred at 80 °C in a sealed tube for 2h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.66 mmol, 73 % yield) as a clear oil: LCMS (ES) m/z = 277 $(M+H)^+$.

c) methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



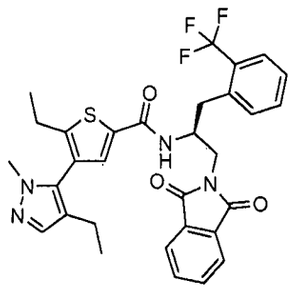
To a solution of methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.68 mmol) in methanol (2.5 ml) was added Pd-C (7.20 mg, 0.07 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (187 mg, 0.64 mmol, 95 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

d) 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



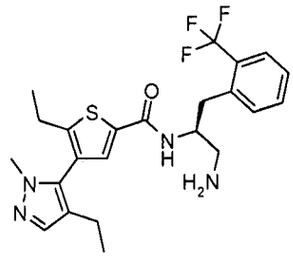
A solution of methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (181 mg, 0.65 mmol) in 6N sodium hydroxide (2.16 ml, 13.0 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (175 mg, 0.65 mmol, 100 % yield) as a white foam: LCMS (ES) m/e 265 $(M+H)^+$.

e) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



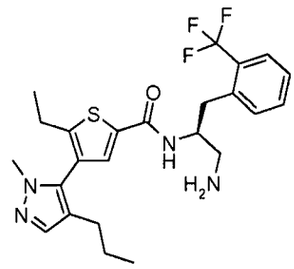
To a solution of 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (175 mg, 0.66 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (255 mg, 0.66 mmol)[prepared according to Procedure 6] and N,N-diisopropylethylamine (0.58 ml, 3.31 mmol) in Dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (340 mg, 0.73 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (232 mg, 0.38 mmol, 57 % yield) as a clear oil: LCMS (ES) m/e 595 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (232 mg, 0.39 mmol) in tetrahydrofuran (2 mL) and methanol (2 mL) at 25 °C was added hydrazine (122 µl, 3.90 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (176 mg, 0.38 mmol, 97 % yield) as a yellow solid: LCMS (ES) m/z = 529, 531 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 (br. s., 1 H) 7.97 (br. s., 3 H) 7.65 - 7.73 (m, 3 H) 7.57 (d, *J*=5.05 Hz, 2 H) 7.59 (br. s., 1 H) 7.44 (br. s., 1 H) 4.48 (br. s., 1 H) 3.69 (s, 3 H) 2.98 - 3.12 (m, 4 H) 1.24 (dd, *J*=6.82, 2.27 Hz, 3 H) 1.16 (dd, *J*=6.82, 2.53 Hz, 3 H).

Example 124

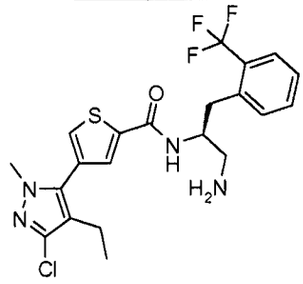


Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to Example 123, except substituting (1Z)-1-propen-1-ylboronic acid (78 mg, 0.91 mmol) for 2,4,6-trivinylcycloboroxane-pyridine complex: LCMS (ES) m/z = 479 (M+H)$^+$, ^{1}H

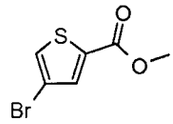
NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (s, 1 H) 8.01 (br. s., 3 H) 7.67 (s, 2 H) 7.56 (d, *J*=5.05 Hz, 2 H) 7.38 - 7.46 (m, 2 H) 4.42 - 4.47 (m, 1 H) 3.59 (s, 3 H) 2.98 - 3.02 (m, 4 H) 2.66 - 2.71 (m, 2 H) 1.40 - 1.47 (m, 2 H) 1.13 (t, *J*=7.52 Hz, 3 H) 0.83 (t, *J*=7.26 Hz, 3 H).

Example 125



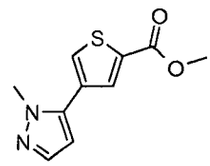
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-bromo-2-thiophenecarboxylate



To a solution of 4-bromo-2-thiophenecarboxylic acid (25 g, 121 mmol) in methanol (241 ml) was added sulfuric acid (32 ml, 604 mmol). The resulting solution stirred at 50 °C over 4d. The solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4-bromo-2-thiophenecarboxylate (26 g, 118 mmol, 97 % yield), LCMS (ES) m/e 222 $(M+H)^+$.

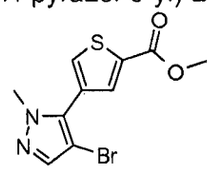
b) methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-bromo-2-thiophenecarboxylate (2.5 g, 11.31 mmol), potassium carbonate (7.81 g, 56.5 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-

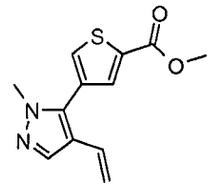
dioxaborolan-2-yl)-1H-pyrazole (2.59 g, 12.44 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.289 g, 0.56 mmol) in 1,4-dioxane (47 ml) and water (9 ml) was stirred at 80 °C in a sealed tube for 1h. 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.59 g, 12.44 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.289 g, 0.56 mmol) were added and the reaction stirred an additional 1h. The mixture was partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-40% EtOAc in hexanes) affording methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.5 g, 11.25 mmol, 99 % yield) as a yellow solid: LCMS (ES) m/e 223 $(M+H)^+$.

c) methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.5 g, 11.25 mmol) and n-bromosuccinimide (2.002 g, 11.25 mmol) in tetrahydrofuran (56.2 ml) was stirred in a sealed tube for 1h at 70 °C. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (10-50% EtOAc in hexanes yielding methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.7 g, 8.97 mmol, 80 % yield) as a yellow solid: LCMS (ES) m/e 301, 303 (M, M+2)$^+$.

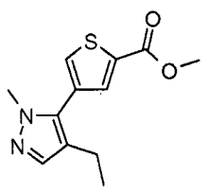
d) methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (300 mg, 0.91 mmol), potassium carbonate (630 mg, 4.56 mmol), bis(tri-t-butylphosphine)palladium(0) (23 mg, 0.05 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (110 mg, 0.46 mmol) in 1,4-dioxane (5 ml)

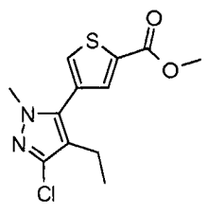
and water (1 ml) was stirred at 80 °C in a sealed tube for 2h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.66 mmol, 73 % yield) as a clear oil: LCMS (ES) m/z = 277 $(M+H)^+$.

e) methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (187 mg, 0.68 mmol) in methanol (2.5 ml) was added Pd-C (7.20 mg, 0.07 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (187 mg, 0.64 mmol, 95 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 279 $(M+H)^+$.

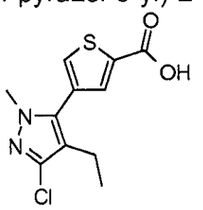
f) methyl 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (202 mg, 0.81 mmol) and NCS (108 mg, 0.81 mmol) in N,N-dimethylformamide (4 ml) was stirred in a sealed tube for 1h at 100 °C. Additional NCS (108 mg, 0.81 mmol) was added and the solution stirred 1h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (2-30% EtOAc in hexanes) affording methyl 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-

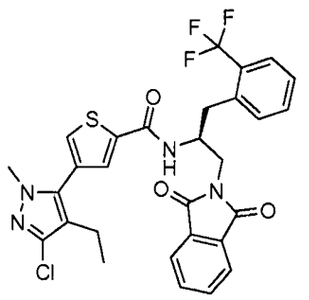
thiophenecarboxylate (135 mg, 0.45 mmol, 56 % yield) as a yellow oil: LCMS (ES) m/e 285 $(M+H)^+$.

g) 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (135 mg, 0.47 mmol) in 6N sodium hydroxide (1.6 ml, 9.48 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 12h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (120 mg, 0.41 mmol, 87 % yield) as a white foam: LCMS (ES) m/e 270, 272 (M, M+2)$^+$.

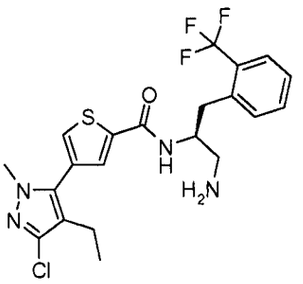
h) 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (120 mg, 0.44 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (171 mg, 0.44 mmol)[prepared according to Preparation 6] and n,n-diisopropylethylamine (0.39 ml, 2.22 mmol) in Dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (228 mg, 0.49 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(3-chloro-4-

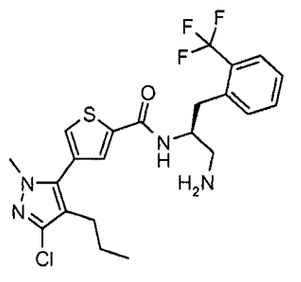
ethyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (190 mg, 0.30 mmol, 68 % yield) as a white solid: LCMS (ES) m/e 601, 603 (M, M+2)$^+$.

i) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (190 mg, 0.32 mmol) in tetrahydrofuran (1.58 ml) and methanol (1.58 ml) at 25 °C was added hydrazine (0.08 ml, 2.53 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in Ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (145 mg, 0.26 mmol, 83 % yield) as a yellow solid: LCMS (ES) m/z = 471, 473 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (br. s., 1 H) 7.87 - 7.99 (m, 6 H) 7.69 (d, J=7.71 Hz, 1H)) 7.57 (d, *J*=7.83 Hz, 1 H) 7.40 - 7.44 (m, 1 H) 4.43 - 4.48 (m, 1 H) 3.74 (s, 3 H) 2.99 - 3.06 (m, 4 H) 2.40 (d, *J*=7.58 Hz, 2 H) 1.04 (t, *J*=7.58 Hz, 3 H).

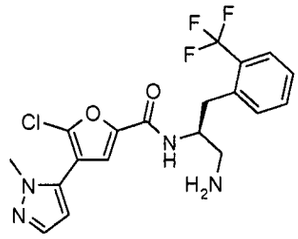
Example 126



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

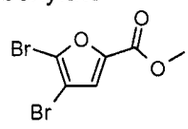
The title compound was prepared as a yellow solid according to Example 125, except substituting (1Z)-1-propen-1-ylboronic acid (125 mg, 1.46 mmol) for 2,4,6-trivinylcycloboroxane-pyridine complex: LCMS (ES) m/z = 485, 487 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.94 (d, *J*=9.09 Hz, 1 H) 8.05 (s, 4 H) 7.98 (s, 1 H) 7.69 (d, *J*=7.58 Hz, 1 H) 7.55 - 7.63 (m, 1 H) 7.52 (t, *J*=7.58 Hz, 1 H) 7.42 (t, *J*=7.33 Hz, 1 H) 4.49 (d, *J*=4.29 Hz, 1 H) 3.74 (s, 3 H) 2.98 - 3.09 (m, 4 H) 2.37 (q, *J*=7.07 Hz, 2 H) 1.37 - 1.45 (m, 2 H) 0.80 (t, *J*=7.33 Hz, 3 H).

Example 127



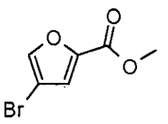
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4,5-dibromo-2-furancarboxylate



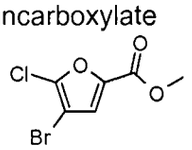
To a solution of 4,5-dibromo-2-furancarboxylic acid (25 g, 93 mmol) in methanol (185 ml) was added sulfuric acid (24.7 ml, 463 mmol). The resulting solution stirred at 50 °C over 12h. The solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification providing methyl 4,5-dibromo-2-furancarboxylate (23.67 g, 83 mmol, 90 % yield), LCMS (ES) m/e 283, 285, 287 (M, M+2, M+4)$^+$.

b) methyl 4-bromo-2-furancarboxylate



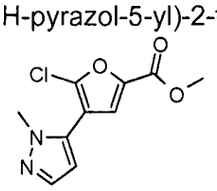
To a solution of methyl 4,5-dibromo-2-furancarboxylate (3.3 g, 11.62 mmol) in tetrahydrofuran (46 ml) at -40 °C was added isopropylmagnesium chloride (6.97 ml, 13.95 mmol). After 1h, Water (11 ml) was added and the solution warmed to 25 °C. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified by column chromatography (3% EtOAc in hexanes) affording methyl 4-bromo-2-furancarboxylate (1.4 g, 6.49 mmol, 56 % yield) as a yellow solid: LCMS (ES) m/e 205, 207 (M, M+2)$^+$.

c) methyl 4-bromo-5-chloro-2-furancarboxylate



A solution of methyl 4-bromo-2-furancarboxylate (1.4 g, 6.83 mmol) and NCS (0.912 g, 6.83 mmol) in N,N-dimethylformamide (13.7 ml) was stirred in a sealed tube for 1h at 100 °C. After 1h, the solution was partitioned between DCM-H_2O and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (2-10% EtOAc in hexanes) affording methyl 4-bromo-5-chloro-2-furancarboxylate (1.348 g, 5.12 mmol, 75 % yield) as a white solid: LCMS (ES) m/e 238, 240, 242 (M, M+2, M+4)$^+$.

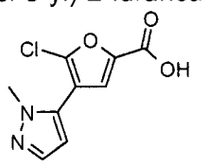
d) methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



A solution of methyl 4-bromo-5-chloro-2-furancarboxylate (1.1 g, 4.59 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.05 g, 5.05 mmol)[prepared according to Preparation 7], potassium carbonate (3.17 g, 22.97 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.117 g, 0.23 mmol) in 1,4-dioxane (19.14 ml) and water (3.83 ml) was stirred at 80 °C in a sealed tube for 1h. The reaction mixture was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried

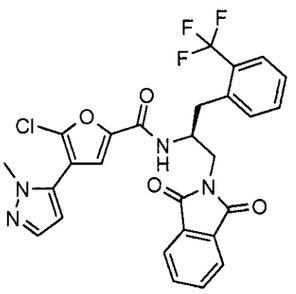
over Na_2SO_4, concentrated and purified via column chromatography (silica, 4-25% EtOAc in hexanes) yielding methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (800 mg, 2.53 mmol, 55 % yield) as a yellow oil: LCMS m/e ES 240, 242 (M, M+2)$^+$.

e) 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



A solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.25 mmol) in 6N sodium hydroxide (4.16 ml, 24.93 mmol) and tetrahydrofuran (5.4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (267 mg, 0.59 mmol, 47 % yield) as a white foam: LCMS (ES) m/e 265 (M+H)$^+$.

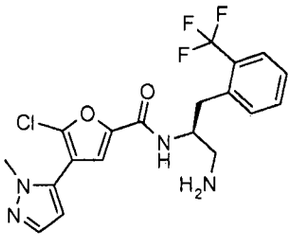
f) 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



To a solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (134 mg, 0.59 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (228 mg, 0.59 mmol)[prepared according to Preparation 6] and N,N-diisopropylethylamine (0.52 ml, 2.96 mmol) in Dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (304 mg, 0.65 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-

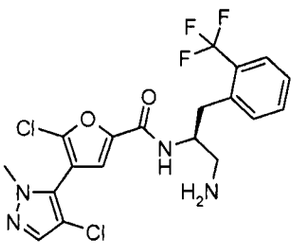
furancarboxamide (202 mg, 0.33 mmol, 55.8 % yield) as a yellow oil: LCMS (ES) m/e 557, 559 $(M, M+2)^+$.

g) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



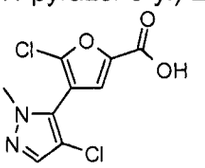
To a solution of 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (202 mg, 0.36 mmol) in tetrahydrofuran (1.8 ml) and methanol (1.8 ml) at 25 °C was added hydrazine (0.08 ml, 2.54 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (2% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 2M HCl in diethyl ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (120 mg, 0.24 mmol, 66 % yield) as a yellow solid: LCMS (ES) m/z = 427, 429 $(M, M+2)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, *J*=9.09 Hz, 1 H) 8.11 (br. s., 3 H) 7.66 - 7.73 (m, 2 H) 7.57 (t, *J*=7.45 Hz, 2 H) 7.53 (d, *J*=1.52 Hz, 1 H) 7.44 (d, *J*=6.82 Hz, 1 H) 6.50 (d, *J*=1.52 Hz, 1 H) 4.43 - 4.51 (m, 1 H) 3.86 (s, 3 H) 2.99 - 3.17 (m, 4H).

Example 128



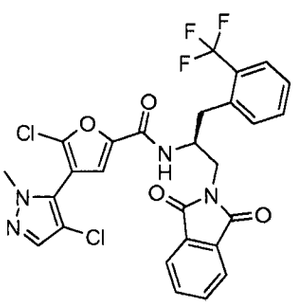
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid



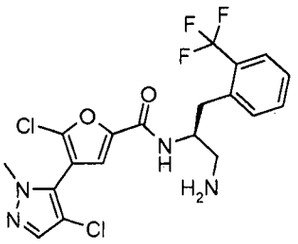
A solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.25 mmol)[prepared according to Example 127] and n-chlorosuccinimide (166 mg, 1.25 mmol) in tetrahydrofuran (6 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (4.1 ml, 24.94 mmol) was added in one portion and the solution stirred an additional 12h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (232 mg, 0.44 mmol, 36 % yield) as a yellow oil: LCMS (ES) m/e 261, 263 (M, M+2)$^+$.

b) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-furancarboxamide



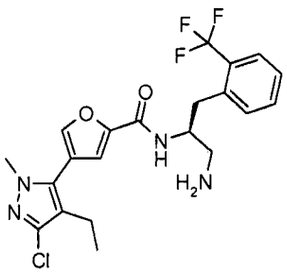
To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (116 mg, 0.44 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (171 mg, 0.44 mmol)[prepared according to Preparation 6] and n,n-diisopropylethylamine (0.39 ml, 2.22 mmol) in dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (228 mg, 0.49 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-furancarboxamide (116 mg, 0.19 mmol, 42 % yield) as a yellow oil: LCMS (ES) m/e 591, 593 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide



To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-furancarboxamide (116 mg, 0.20 mmol) in tetrahydrofuran (1 ml) and methanol (1 ml) at 25 °C was added hydrazine (0.04 ml, 1.37 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (2% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 2M HCl in Ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (68 mg, 0.13 mmol, 65 % yield) as a yellow solid: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (d, *J*=9.09 Hz, 1 H) 8.03 (br. s., 3 H) 7.66 - 7.73 (m, 2 H) 7.58 - 7.61 (m, 1 H) 7.52 - 7.59 (m, 2 H) 7.40 - 7.48 (m, 1 H) 4.5 - 4.57 (m, 1 H) 3.77 (s, 3 H) 2.98 - 3.09 (m, 4 H).

Example 129

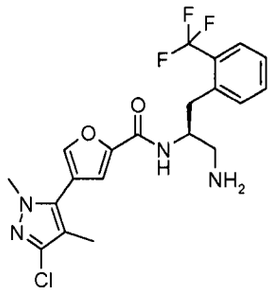


Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to Example 125, except substituting methyl 4-bromo-2-furancarboxylate (5 g, 24.39 mmol) for methyl 4-bromo-2-thiophenecarboxylate: LCMS (ES) m/z = 455, 457 (M, M+2)$^+$,

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (d, J=9.09 Hz, 1 H) 8.23 (s, 1 H) 8.05 (br. s., 3 H) 7.70 (d, J=7.83 Hz, 1 H) 7.53 - 7.60 (m, 2 H) 7.42=0 - 7.43 (m, 2 H) 4.50 - 4.55 (m, 1 H) 3.74 (s, 3 H) 2.99 - 3.08 (m, 4 H) 2.39 (q, J=7.33 Hz, 2 H) 1.03 (t, J=7.45 Hz, 3 H).

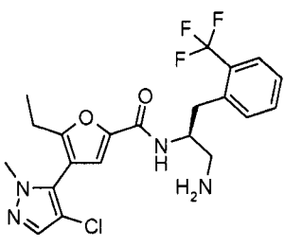
Example 130



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

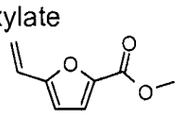
The title compound was prepared as a yellow solid according to Example 125, except substituting trimethylboroxine (0.78 ml, 5.61 mmol) for 2,4,6-trivinylcycloboroxane-pyridine complex and methyl 4-bromo-2-furancarboxylate (5 g, 24.39 mmol) for methyl 4-bromo-2-thiophenecarboxylate: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (d, J=9.35 Hz, 1 H) 8.27 (s, 1 H) 8.01 (br. s., 3 H) 7.70 (d, J=7.58 Hz, 1 H) 7.55 (t, J=6.06 Hz, 2 H) 7.40 - 7.47 (m, 2 H) 4.50 - 4.57 (m, 1 H) 3.78 (s, 3 H) 2.99 - 3.08 (m, 4 H) 1.98 (s, 3 H).

Example 131



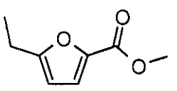
Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide

a) methyl 5-ethenyl-2-furancarboxylate



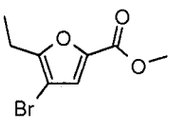
A solution of methyl 5-bromo-2-furancarboxylate (2.5 g, 12.19 mmol), potassium carbonate (8.43 g, 61.0 mmol), bis(tri-t-butylphosphine)palladium(0) (0.312 g, 0.61 mmol) and 2,4,6-trivinylcycloboroxane-pyridine complex (1.47 g, 6.10 mmol) in 1,4-dioxane (50 ml) and water (10 ml) was stirred at 80 °C in a sealed tube for 2h. The reaction contents were partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-ethenyl-2-furancarboxylate (1.3 g, 7.09 mmol, 58 % yield) as a yellow oil: LCMS (ES) m/z = 153 $(M+H)^+$.

b) methyl 5-ethyl-2-furancarboxylate



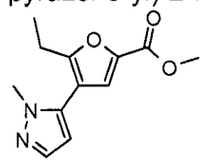
To a solution of methyl 5-ethenyl-2-furancarboxylate (1.3 g, 8.54 mmol) in methanol (15 ml) was added $PdOH_2$ (0.240 g, 1.71 mmol). The reaction mixture was hydrogenated at 1 atm (balloon) for 1h. The solution was then purged with N_2, filtered through Celite and concentrated affording methyl 5-ethyl-2-furancarboxylate (1.2 g, 7.16 mmol, 84 % yield) as a clear oil which was used without further purification: LCMS (ES) m/e 155 $(M+H)^+$.

c) methyl 4-bromo-5-ethyl-2-furancarboxylate



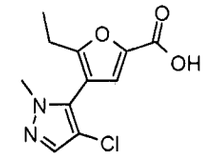
To a solution of methyl 5-ethyl-2-furancarboxylate (1.2 g, 7.78 mmol) and aluminum trichloride (1.56 g, 11.68 mmol) in chloroform (15 ml) at 25 °C was added bromine (0.56 ml, 10.90 mmol). The resulting solution stirred at 70 °C in a sealed tube for 2h and the solution was cooled, concentrated and purified via column chromatograpy (silica, 5% EtOAc in hexanes) affording methyl 4-bromo-5-ethyl-2-furancarboxylate (1.1 g, 3.26 mmol, 41.8 % yield) as a white solid; LCMS (ES) m/z = 233, 235 (M, M+2)$^+$.

d) methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



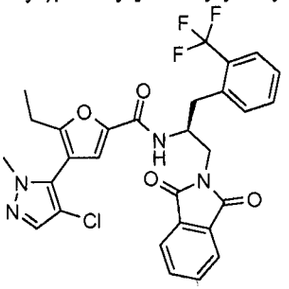
A solution of methyl 4-bromo-5-ethyl-2-furancarboxylate (1.1 g, 4.72 mmol), potassium carbonate (3.26 g, 23.60 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.178 g, 5.66 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.121 g, 0.24 mmol) were combined in a sealed tube and stirred at 80 °C for 1h. LCMS showed 4:1 pdt/sm. Additional 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.178 g, 5.66 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.121 g, 0.24 mmol) were added and the solution stirred an additional 2h where crude LCMS showed nearly complete conversion to product. The reaction contents were then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (950 mg, 3.37 mmol, 71.3 % yield) as a yellow oil: LCMS (ES) m/e 235 $(M+H)^+$.

e) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxylic acid



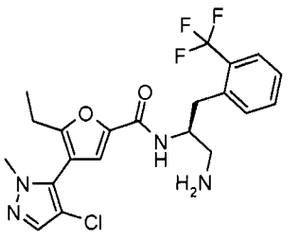
A solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (950 mg, 4.06 mmol) and N-chlorosuccinimide (542 mg, 4.06 mmol) in tetrahydrofuran (20 ml) was stirred in a sealed tube for 1h at 70 °C. 6N sodium hydroxide (13.5 ml, 81 mmol) was added in one portion and the solution stirred an additional 1h. The reaction mixture was then partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4 and washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and used directly without further purification yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxylic acid (683 mg, 2.55 mmol, 62.8 % yield) as a yellow oil: LCMS (ES) m/e 254, 256 (M, M+2)$^+$.

f) 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-furancarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxylic acid (145 mg, 0.57 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (219 mg, 0.57 mmol)[prepared according to Preparation 6] and N,N-diisopropylethylamine (0.50 ml, 2.85 mmol) in dichloromethane (4.6 ml) at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (292 mg, 0.63 mmol) in one portion. The solution stirred at 25 °C for 1h and was then dry loaded onto silica and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-furancarboxamide (250 mg, 0.41 mmol, 71 % yield) as a white solid: LCMS (ES) m/e 585, 587 (M, M+2)$^+$.

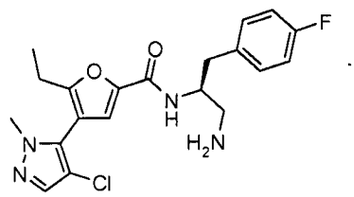
g) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide



To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-2-furancarboxamide (250 mg, 0.43 mmol) in tetrahydrofuran (1.8 ml) and methanol (1.8 ml) at 25 °C was added hydrazine (0.13 ml, 4.27 mmol) dropwise. After 12h the solution was concentrated, dry loaded onto silica and purified by column chromatography (2% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 2M HCl in Ether (2 ml) to the residue in DCM (2 ml) affording the HCl salt of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-

2-furancarboxamide (166 mg, 0.30 mmol, 70 % yield) as a yellow solid: LCMS (ES) m/z = 455, 457 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.59 (br. s., 1 H) 8.06 (br. s., 3 H) 7.67 (s, 1 H) 7.70 (d, *J*=7.83 Hz, 1 H) 7.59 (d, *J*=4.29 Hz, 2 H) 7.44 (d, *J*=4.04 Hz, 1 H) 7.31 (d, *J*=5.81 Hz, 1 H) 4.50 - 4.57 (m, 1 H) 3.72 (s, 3 H) 2.99 - 3.12 (m, 4 H) 2.63 (q, *J*=7.33 Hz, 2 H) 1.21 (t, *J*=7.45 Hz, 3 H).

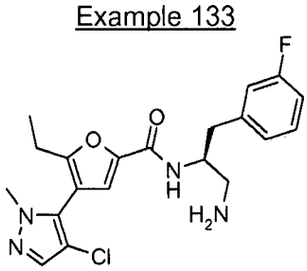
Example 132



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide

The title compound was prepared as a yellow solid according to Example 131, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (170 mg, 0.57 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 405, 407(M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 8.56 (d, J=8.59 Hz, 1 H) 8.09 (br. s., 3 H) 7.67 (s, 1 H) 7.33 (s, 1 H) 7.31 (dd, J=8.34, 5.81 Hz, 2 H) 7.12 (t, J=8.72 Hz, 2 H) 4.36 - 4.39 (m, 1 H) 3.71 (s, 3 H) 2.91 - 3.03 (m, 4 H) 2.62 (q, J=7.58 Hz, 2 H) 1.20 (t, J=7.45 Hz, 3 H).

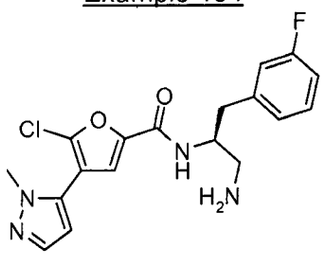
Example 133



Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide

The title compound was prepared as a yellow solid according to Example 131, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (170 mg, 0.57 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 405, 407 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.62 (d, *J*=8.59 Hz, 1 H) 8.13 (br. s., 3 H) 7.67 (s, 1 H) 7.30 - 7.37 (m, 2 H) 7.12 (d, *J*=6.32 Hz, 2 H) 7.04 (t, *J*=8.59 Hz, 1 H) 4.40 - 4.47 (m, 1 H) 3.71 (s, 3 H) 2.95 - 3.09 (m, 4 H) 2.62 (q, *J*=7.07 Hz, 2 H) 1.20 (t, *J*=7.33 Hz, 3 H).

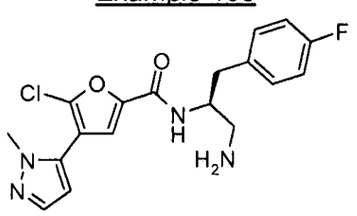
Example 134



Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 127, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (295 mg, 0.88 mmol)[prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 377, 379 (M, M+2)$^+$, 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, *J*=8.84 Hz, 1 H) 8.16 (br. s., 3 H) 7.70 - 7.77 (m, 1 H) 7.53 (d, *J*=1.77 Hz, 1 H) 7.32 (t, *J*=7.20 Hz, 1 H) 7.09 - 7.14 (m, 1 H) 7.11 (d, *J*=6.57 Hz, 2 H) 7.04 (t, *J*=8.59 Hz, 1 H) 6.49 (d, *J*=1.77 Hz, 1 H) 4.41 - 4.44 (m, 1 H) 3.86 (s, 3 H) 2.95 - 3.00 (m, 4 H).

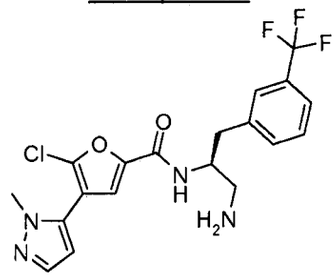
Example 135



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 127, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (295 mg, 0.88 mmol)[prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 377, 379 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.80 (d, *J*=8.84 Hz, 1 H) 8.11 (br. s., 3 H) 7.71 (s, 1 H) 7.53 (d, *J*=1.77 Hz, 1 H) 7.29 (dd, *J*=8.59, 5.56 Hz, 2 H) 7.12 (t, *J*=8.84 Hz, 2 H) 6.49 (d, *J*=1.77 Hz, 1 H) 4.32 - 4.38 (m, 1 H) 3.86 (s, 3 H) 2.99 - 3.01 (m, 4 H).

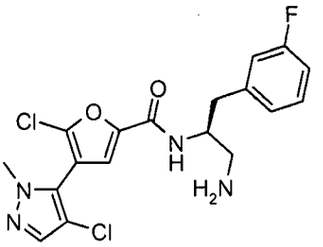
Example 136



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 127, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (340 mg, 0.88 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 427, 429 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (d, *J*=8.84 Hz, 1 H) 8.11 (br. s., 3 H) 7.62 - 7.69 (m, 2 H) 7.51 - 7.59 (m, 4 H) 6.48 (d, *J*=1.77 Hz, 1 H) 4.39 - 4.44 (m, 1 H) 3.85 (s, 3 H) 2.97 - 3.05 (m, 4 H).

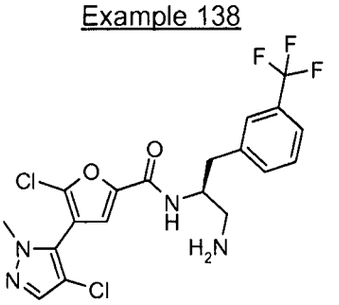
Example 137



Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 128, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (321 mg, 0.96 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 411, 413 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.77 (d, J=8.84 Hz, 1 H) 8.04 (br. s., 3 H) 7.72 (s, 1 H) 7.59 (s, 1 H) 7.30 - 7.38 (m, 1 H) 7.11 (d, J=7.58 Hz, 2 H) 7.05 (t, J=8.59 Hz, 1 H) 4.39 - 4.43 (m, 1 H) 3.77 (s, 3 H) 2.97 - 3.03 (m, 4 H).

Example 138

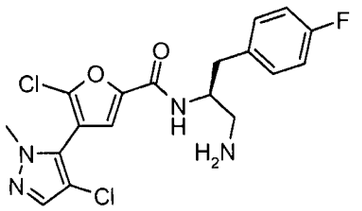


Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 128, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (221 mg, 0.58 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (d, J=8.84 Hz, 1 H)

8.10 (br. s., 3 H) 7.72 (s, 1 H) 7.64 (s, 1 H) 7.52 - 7.60 (m, 4 H) 4.39 - 4.41 (m, 1 H) 3.76 (s, 3 H) 2.98 - 3.05 (m, 4 H).

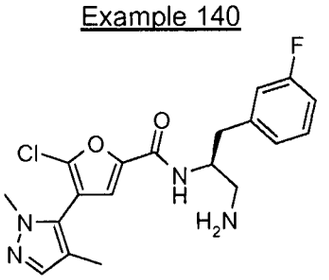
Example 139



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white foam according to the procedure of Example 128, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (256 mg, 0.77 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 411, 413 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.78 (d, J=8.59 Hz, 1 H) 8.06 (br. s., 3 H) 7.72 (s, 1 H) 7.60 (s, 1 H) 7.30 (dd, J=8.59, 5.56 Hz, 2 H) 7.13 (t, J=8.84 Hz, 2 H) 4.35 - 4.42 (m, 1 H) 3.77 (s, 3 H) 2.99 (br. s., 2 H) 2.86 - 2.93 (m, 2 H).

Example 140

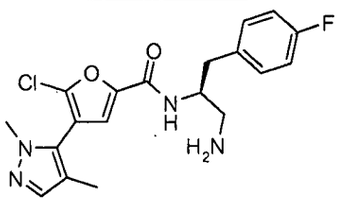


Preparation of N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.02 g, 4.59 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-

pyrazole and 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (132 mg, 0.39 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 391, 393 $(M, M+2)^+$, 1H NMR (400 MHz, DMSO-d_6) δ ppm 8.75 (d, *J*=8.84 Hz, 1 H) 8.04 (br. s., 3 H) 7.55 (s, 1 H) 7.37 (s, 1 H) 7.30 - 7.36 (m, 1 H) 7.11 - 7.15 (m, 2 H) 7.05 - 7.10 (m, 1 H) 4.42 (br. s., 1 H) 3.70 (s, 3 H) 2.97 (br. s., 2 H) 2.92 - 2.96 (m, 2 H) 1.94 (s, 3 H).

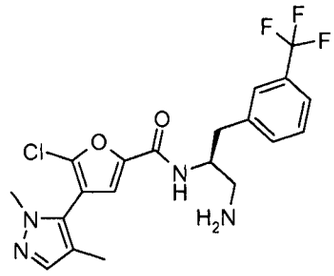
Example 141



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.06 g, 13.78 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (174 mg, 0.52 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 391, 393 $(M, M+2)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.81 (d, *J*=8.59 Hz, 1 H) 8.14 (br. s., 3 H) 7.59 (s, 1 H) 7.37 (s, 1 H) 7.30 (dd, *J*=8.59, 5.56 Hz, 2 H) 7.12 (t, *J*=8.84 Hz, 2 H) 4.32 - 4.38 (m, 1 H) 3.70 (s, 3 H) 2.98 (d, *J*=5.81 Hz, 2 H) 2.91 (d, *J*=6.32 Hz, 2 H) 1.94 (s, 3 H).

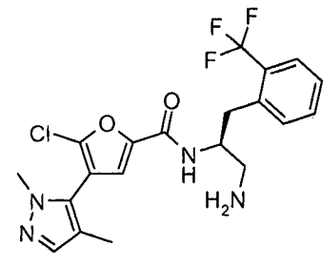
Example 142



Preparation of N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.06 g, 13.78 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (200 mg, 0.52 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.83 (br. s., 1 H) 8.15 (br. s., 2 H) 7.63 (br. s., 1 H) 7.52 - 7.58 (m, 4 H) 7.37 (s, 1 H) 4.38 - 4.42 (m, 1 H) 3.68 (s, 3 H) 2.97 - 3.08 (m, 4 H) 1.93 (s, 3 H).

Example 143

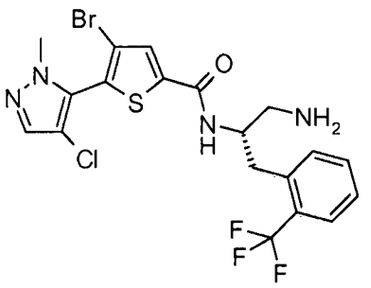


Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 127, except substituting 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (3.06 g, 13.78 mmol)[prepared according to Preparation 17] for 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-

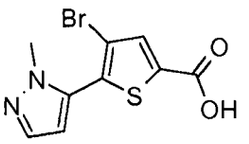
1,3(2H)-dione (200 mg, 0.52 mmol) [prepared according the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.87 (d, *J*=9.35 Hz, 1 H) 8.11 (br. s., 3 H) 7.70 (d, *J*=7.83 Hz, 1 H) 7.52 - 7.57 (m, 3 H) 7.41 - 7.47 (m, 1 H) 7.38 (s, 1 H) 4.39 - 4.43 (m, 1 H) 3.71 (s, 3 H) 2.98 - 3.09 (m, 4 H) 1.95 (s, 3 H).

Example 144



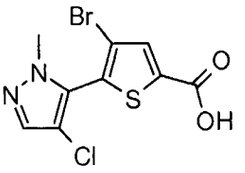
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



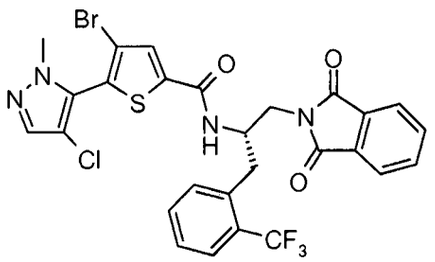
To a solution of 4,5-dibromo-2-thiophenecarboxylic acid (3.30 g, 11.54 mmol) in dioxane/H_2O (4:1, 100 mL) was added K_2CO_3 (5.5 g, 40.0 mmol), tetrakistriphenylphosphine Pd(0) (671 mg, 0.58 mmol) and 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methyl-1*H*-pyrazole (2.66 g, 13.71 mmol). The reaction mixture was heated to 80 °C in a sealed tube for 12 hours. The reaction mixture was partitioned between H_2O and $CHCl_3$. The pH of the aqueous phase was adjusted to ~3 with 6N HCl and washed several times with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (3.3 g, quant.): LC-MS (ES) m/z = 289 (M+H)$^+$.

b) 4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



N-chlorosuccinimide (NCS) (299 mg, 2.194 mmol) was added in portions to a 30 mL sealed tube reactor containing 4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (503 mg, 1.23 mmol) in tetrahydrofuran (THF) (6 mL) at room temperature. The mixture was heated to 70 °C for 2 hours. Upon completion, the reaction mixture was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4, solvents removed by vacuum distillation affording the title compound (0.54 mg, quant.) which was used without further purification. LC-MS (ES) m/z = 321 $(M+H)^+$

c) 4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



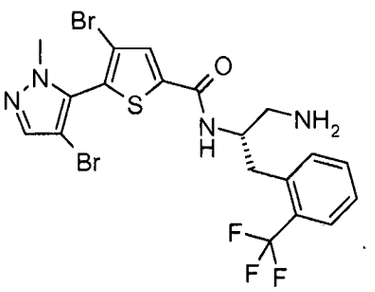
To a 50 mL round-bottomed flask was added 4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (224 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (201 mg, 0.52 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (295 mg, 0.63 mmol) in chloroform (4 mL). DIEA (0.46 mL, 2.63 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (hexanes/EtOAc) affording the title compound (153 mg, 43%): LC-MS (ES) m/z = 651 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (153 mg, 0.223 mmol) in tetrahydrofuran (THF) (2.5 mL) and Methanol (0.5 mL). Hydrazine (50 µL, 1.59 mmol) was added and the mixture stirred overnight at room temperature. Upon completion, the mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

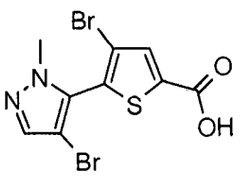
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (68 mg, 0.11 mmol, 48.7 % yield): LC-MS (ES) m/z = 523 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.02 - 3.14 (m, 4 H) 3.73 (s, 3 H) 4.50 (s, 1 H) 7.40 - 7.48 (m, 1 H) 7.56 - 7.64 (m, 2 H) 7.71 (d, *J*=7.83 Hz, 1 H) 7.77 (s, 1 H) 8.14 (s, 3 H) 8.21 (s, 1 H) 9.24 (d, *J*=9.09 Hz, 1 H).

Example 145



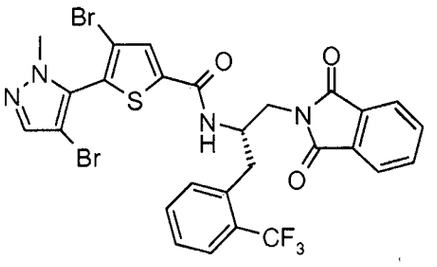
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



The title compound was prepared according to the procedure of Example 144 except substituting N-bromosuccinimide (NBS) (287 mg, 1.596 mmol) for NCS: LC-MS (ES) m/z = 364 $(M+H)^+$.

b) 4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-bromo-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (238 mg, 0.52 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (209 mg, 0.54 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (293 mg, 0.63 mmol) in chloroform (4 mL). DIEA (0.46 mL, 2.62 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (silica) (3:1 hex/EtOAc) affording the title compound (229 mg, 60%): LC-MS (ES) m/z = 695 $(M+H)^+$.

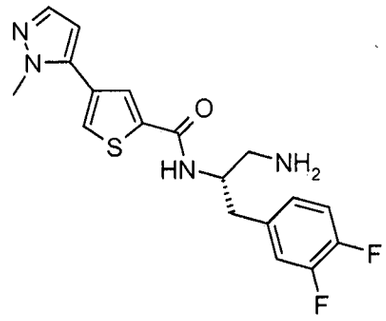
c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-bromo-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (229 mg, 0.312 mmol) in Tetrahydrofuran (THF) (2.5 mL) and methanol (0.5 mL). Hydrazine (60 µL, 1.91 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica gel and purified by column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH; 12g column).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O (500 mL) and concentrated affording the HCl salt of the title compound(104 mg, 0.15 mmol, 49 % yield): LC-MS (ES) m/z = 567 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.10 (s, 4 H) 3.74 (s, 3 H) 4.50 (s, 1 H) 7.45 (ddd,

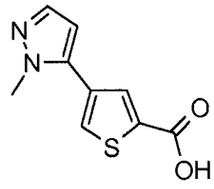
J=7.96, 4.17, 4.04 Hz, 1 H) 7.60 (d, *J*=4.04 Hz, 2 H) 7.71 (d, *J*=7.58 Hz, 1 H) 7.76 (s, 1 H) 8.11 (s, 3 H) 8.19 (s, 1 H) 9.19 (d, *J*=8.84 Hz, 1 H).

Example 146



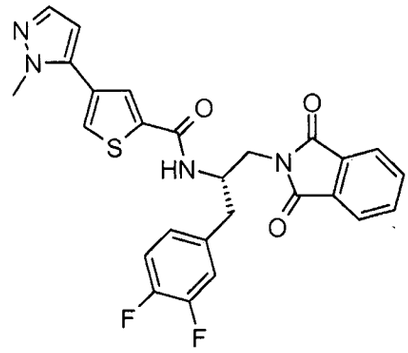
Preparation of N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 4-bromo-2-thiophenecarboxylic acid (3.91 g, 18.9 mmol) in dioxane/H_2O (4:1, 100 mL) was added Cs_2CO_3 (21.7 g, 66.6 mmol), tetrakistriphenylphosphine Pd(0) (1.1 g, 0.95 mmol) and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (3.94 g, 18.94 mmol) [prepared according to the procedure of Preparation 7]. The reaction mixture was heated to 85 °C in a sealed tube for 12 hours and partitioned between H_2O and $CHCl_3$. The pH of the aqueous phase was adjusted to ~3 with 6N HCl and washed several times with $CHCl_3$. The combined organic fractions were dried (Na_2SO_4), concentrated under vacuum and used directly without further purification (2.84 g, 13.64 mmol, 72%): LC-MS (ES) m/z = 209 $(M+H)^+$.

b) *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (183 mg, 0.88 mmol), 2-[(2S)-2-amino-3-(3,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (0.3 g, 0.85 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3,4-difluoro-L-phenylalanine (2.03 g, 6.74 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (528 mg, 1.13 mmol) in chloroform (5 mL). DIEA (0.77 mL, 4.41 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (149 mg, 30%): LC-MS (ES) m/z = 507 $(M+H)^+$

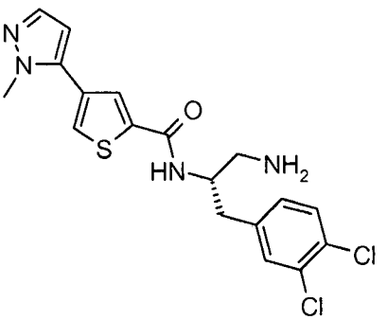
c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (149 mg, 0.265 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (60 µL, 1.91 mmol) was added and the mixture stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (71 mg, 0.15 mmol, 57 % yield): LC-MS (ES) m/z = 377 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.96 (d, *J*=6.06 Hz, 2 H) 3.00 - 3.06 (m, 2 H) 3.97 (s, 3 H) 4.33 - 4.42 (m, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.14 (s, 1 H) 7.30 - 7.42 (m, 2 H) 7.47 (d,

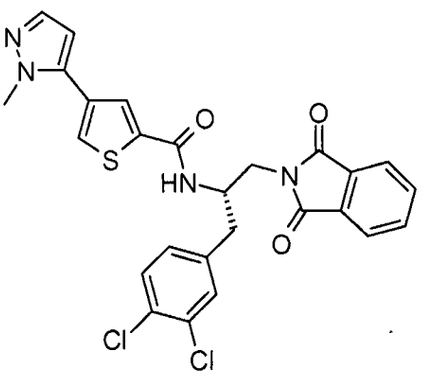
J=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.22 (s, 3 H) 8.35 (d, *J*=1.26 Hz, 1 H) 9.09 (d, *J*=8.59 Hz, 1 H).

Example 147



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(3,4-dichlorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (160 mg, 0.62 mmol) [prepared according to the procedure of Example 146], 2-[(2S)-2-amino-3-(3,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (0.26 g, 0.67 mmol) [prepared according to the procedure of Preparation 6 except substituting 3,4-dichloro-*N*-{[(1,1-dimethylethyl)oxy]carbonyl}-L-phenylalanine (2.03 g, 6.07 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (376 mg, 0.80 mmol) in chloroform (4 mL). DIEA (0.55 mL, 3.15 mmol) was added and

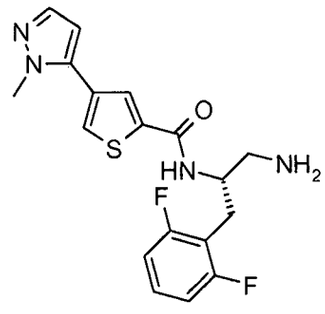
the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (149 mg, 30%): LC-MS (ES) m/z = 539 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(3,4-dichlorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (211 mg, 0.34 mmol) in Tetrahydrofuran (THF) (4.5 mL) and Methanol (0.45 mL). Hydrazine (75 µL, 2.390 mmol) was added and the mixture stirred overnight at room temperature. Upon completion the mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

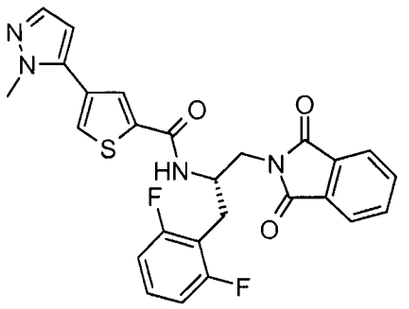
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (83 mg, 0.16 mmol, 48 % yield): LC-MS (ES) m/z = 411 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 - 3.07 (m, 4 H) 3.97 (s, 3 H) 4.32 - 4.43 (m, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.29 (dd, *J*=8.21, 1.89 Hz, 1 H) 7.47 (d, *J*=2.02 Hz, 1 H) 7.54 (d, *J*=8.08 Hz, 1 H) 7.60 (d, *J*=1.77 Hz, 1 H) 8.00 (d, *J*=1.26 Hz, 1 H) 8.22 (s, 3 H) 8.35 (d, *J*=1.01 Hz, 1 H) 9.11 (d, *J*=8.59 Hz, 1 H).

Example 148



Preparation of *N*-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (160 mg, 0.62 mmol) [prepared according to the procedure of Example 146], 2-[(2*S*)-2-amino-3-(2,6-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (231 mg, 0.69 mmol) [prepared according to the procedure of Preparation 18] and PyBrop (353 mg, 0.75 mmol) in chloroform (8 mL). DIEA (0.64 mL, 3.66 mmol) was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (149 mg, 0.21 mmol, 30%): LC-MS (ES) m/z = 507 $(M+H)^+$

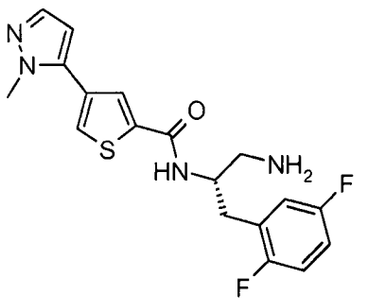
b) *N*-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,6-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (168 mg, 0.32 mmol) in Tetrahydrofuran (THF) (3.6 mL) and Methanol (0.4 mL). Hydrazine (70 µL, 2.23 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (101 mg, 0.214 mmol, 68%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-

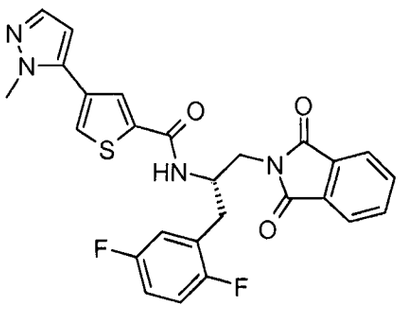
d_6) δ ppm 2.92 - 3.03 (m, 3 H) 3.17 (m, 1 H) 3.97 (s, 3 H) 4.46 (m, 1 H) 6.47 (d, *J*=1.77 Hz, 1 H) 7.05 (t, *J*=7.83 Hz, 2 H) 7.27 - 7.38 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.23 (d, *J*=1.26 Hz, 4 H) 8.92 (d, *J*=8.59 Hz, 1 H).

Example 149



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (257 mg, 0.93 mmol) [prepared according to the procedure of Example 146], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (476 mg, 0.81 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (535 mg, 1.14 mmol) in Chloroform (15 mL). DIEA (0.808 mL, 4.63 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and

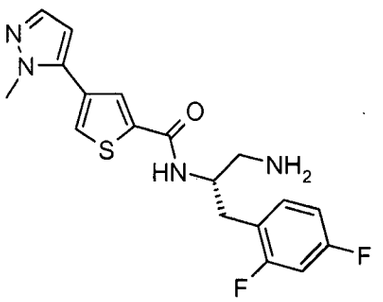
purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (225 mg, 34%): LC-MS (ES) m/z = 507 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (225 mg, 0.31 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (0.8 mL). Hydrazine (60 µL, 1.91 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

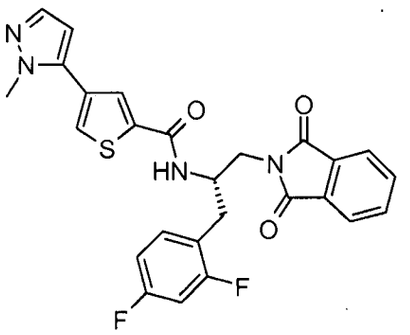
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (90.5 mg, 0.19 mmol, 63%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.95 - 3.01 (m, 2 H) 3.03 - 3.10 (m, 2 H) 3.92 - 3.98 (m, 3 H) 4.41 - 4.51 (m, 1 H) 6.47 (d, *J*=1.77 Hz, 1 H) 7.05 - 7.13 (m, 1 H) 7.20 (td, *J*=9.09, 4.55 Hz, 1 H) 7.27 (ddd, *J*=9.09, 5.81, 3.28 Hz, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.52 Hz, 1 H) 8.18 (s, 3 H) 8.29 (d, *J*=1.26 Hz, 1 H) 9.03 (d, *J*=8.84 Hz, 1 H).

Example 150



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



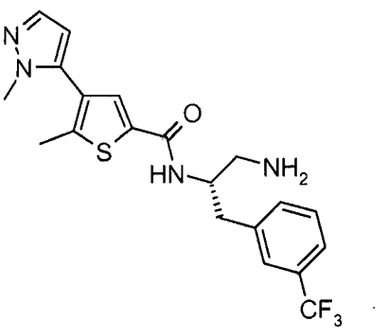
To a 50 mL round-bottomed flask was added 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (222 mg, 0.80 mmol) [prepared according to the procedure of Example 146], 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (331 mg, 0.78 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (1.0 g, 4.97 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (448 mg, 0.96 mmol) in chloroform (10 mL). DIEA (700 µL, 4.01 mmol) was added and the reaction stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 75% EtOAc/Hex) affording the title compound (249 mg, 0.36 mmol, 46%): LC-MS (ES) m/z = 507 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (249 mg, 0.36 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (1 mL). Hydrazine (80 µL, 2.55 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

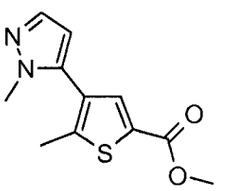
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (81 mg, 0.18 mmol, 50%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 2.98 (m, 2 H) 2.98 - 3.09 (m, 2 H) 3.93 - 3.98 (m, 3 H) 4.38 - 4.47 (m, 1 H) 6.47 (d, *J*=1.77 Hz, 1 H) 7.00 (td, *J*=8.46, 2.27 Hz, 1 H) 7.19 (td, *J*=9.85, 2.53 Hz, 1 H) 7.38 - 7.45 (m, 1 H) 7.47 (d, *J*=1.77 Hz, 1 H) 7.99 (d, *J*=1.26 Hz, 1 H) 8.18 (br. s, 3 H) 8.27 (d, *J*=1.26 Hz, 1 H) 8.99 (d, *J*=8.59 Hz, 1 H).

Example 151



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

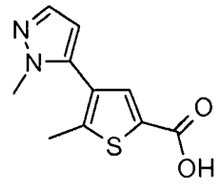
a) methyl 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 125 mL sealed flask was added methyl 4-bromo-5-methyl-2-thiophenecarboxylate (1.56 g, 6.64 mmol) [Prepared according to the procedure of Preparation 10], 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.67 g, 8.03 mmol) [prepared according to the procedure of Preparation 7], K_2CO_3 (2.76 g, 19.97 mmol) and $Pd(PtBu_3)_2$ (170 mg, 0.33 mmol) in 1,4-Dioxane (27 ml) and water (7 ml). The reaction mixture was heated to 85 °C in a sealed tube for 3 hours, cooled to room temperature and partitioned between H_2O and $CHCl_3$. The organic fraction was dried (Na_2SO_4), adsorbed onto silica and purified via

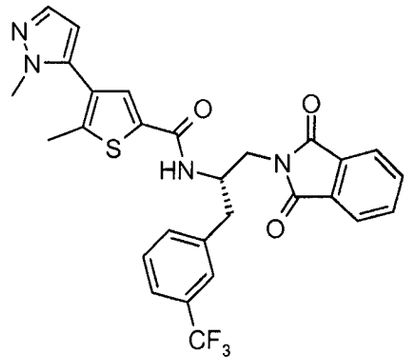
column chromatography (0-15%EtOAc/Hexane). (385 mg, 1.4 mmol, 30%): LC-MS (ES) m/z = 237 $(M+H)^+$.

b) 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1.34 g, 5.67 mmol) in Tetrahydrofuran (THF) (31 ml). 6N NaOH (31 ml, 186 mmol) was added and the reaction mixture stirred at 70 °C overnight. The reaction mixture was neutralized by slow addition of 6N HCl and partitioned between $CHCl_3$ and H_2O. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed. The resulting solid was used without further purification (0.71 g, 2.81 mmol, 96%): LC-MS (ES) m/z = 223 $(M+H)^+$.

c) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (201 mg, 0.91 mmol), 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (301 mg, 0.87 mmol) [Prepared according to Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 14.95 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (519 mg, 1.11 mmol) in chloroform (9 mL). DIEA (790 µL, 4.52 mmol)

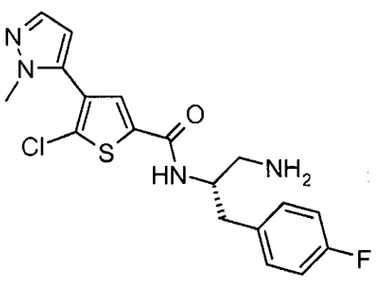
was added and the mixture stirred overnight at room temperature. The reaction mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (247 mg, 45%): LC-MS (ES) m/z = 553 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (374 mg, 0.64 mmol) in Tetrahydrofuran (THF) (6 mL) and Methanol (600 µL). Hydrazine (125 µL, 3.98 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

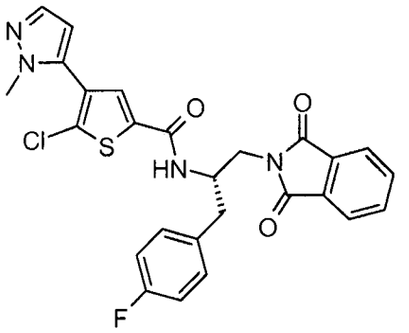
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (135 mg, 0.27 mmol, 42 % yield): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.37 (s, 3 H) 2.95 - 3.11 (m, 4 H) 3.78 (s, 3 H) 4.32 - 4.42 (m, 1 H) 6.34 (d, *J*=1.77 Hz, 1 H) 7.48 - 7.56 (m, 3 H) 7.58 - 7.61 (m, 1 H) 7.67 (s, 1 H) 8.04 (s, 1 H) 8.21 (s, 3 H) 8.98 (d, *J*=8.59 Hz, 1 H).

Example 152



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (201 mg, 0.91 mmol) [prepared according to the procedure of Example 95], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (301 mg, 0.87 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (519 mg, 1.11 mmol) in Chloroform (9 mL). DIEA (790 µL, 4.52 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (186 mg, 32%): LC-MS (ES) m/z = 553 $(M+H)^+$.

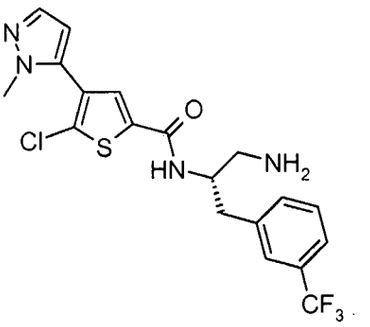
b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (185 mg, 0.34 mmol) in Tetrahydrofuran (THF) (10 mL) and Methanol (1 mL). Hydrazine (63 µL, 2.0 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (101 mg, 0.24 mmol, 72%): LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-

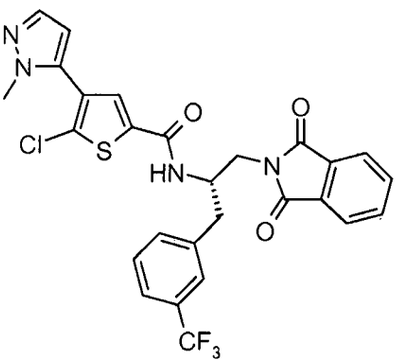
d_6) δ ppm 2.90 - 3.1 (m, 4 H) 3.85 (s, 3 H) 4.33 (s, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.10 (t, *J*=8.84 Hz, 2 H) 7.32 (dd, *J*=8.46, 5.68 Hz, 2 H) 7.55 (d, *J*=2.02 Hz, 1 H) 8.19 (s, 3 H) 8.23 - 8.28 (m, 1 H) 9.25 (d, *J*=8.59 Hz, 1 H).

Example 153



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (226 mg, 0.93 mmol) [prepared according to the procedure of Example 95], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (519 mg, 1.349 mmol) [prepared according to Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop

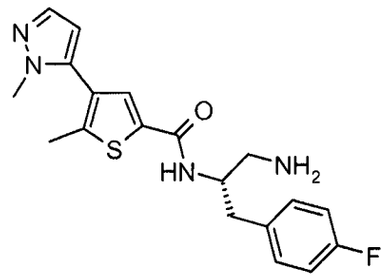
(515 mg, 1.1 mmol) in chloroform (10 mL). DIEA (820 µL, 4.70 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (379 mg, 69%): LC-MS (ES) m/z = 573 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (378 mg, 0.64 mmol) in Tetrahydrofuran (THF) (10 mL) and Methanol (1 mL). Hydrazine (122 µL, 3.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

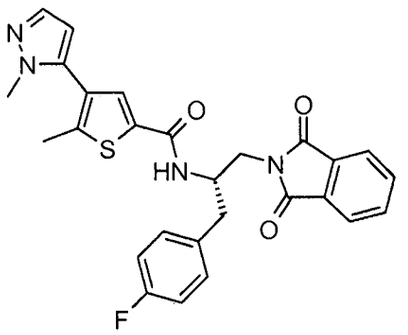
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (222 mg, 0.41 mmol, 64%): LC-MS (ES) m/z = 443 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.05 (d, *J*=6.82 Hz, 4 H) 3.84 (s, 3 H) 4.37 (d, *J*=5.05 Hz, 1 H) 6.46 (d, *J*=1.77 Hz, 1 H) 7.49 - 7.57 (m, 3 H) 7.58 - 7.61 (m, 1 H) 7.67 (s, 1 H) 8.20 (s, 3 H) 8.24 (s, 1 H) 9.31 (d, *J*=8.84 Hz, 1 H).

Example 154



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



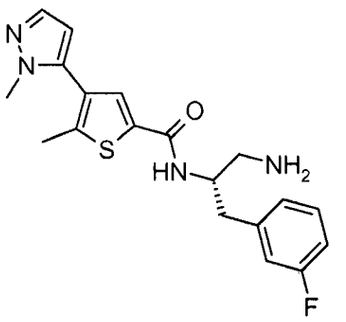
To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (200 mg, 0.90 mmol) [Prepared according to the procedure of Example 151], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (288 mg, 0.86 mmol) [Prepared according to Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (512 mg, 1.09 mmol) in Chloroform (9 mL). DIEA (790 µL, 4.52 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (162 mg, 32%): LC-MS (ES) m/z = 503 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (162 mg, 0.29 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (300 µL). Hydrazine (58 µL, 1.85 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

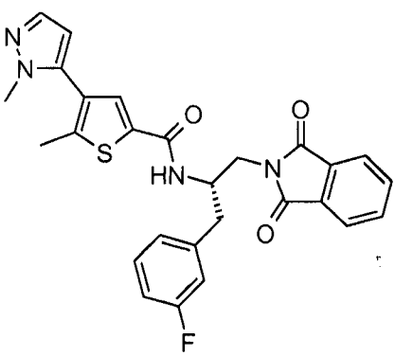
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (222 mg, 0.41 mmol, 64%): LC-MS (ES) m/z = 373 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.89 - 3.02 (m, 4 H) 3.79 (s, 3 H) 4.26 - 4.48 (m, 1 H) 6.36 (d, *J*=1.77 Hz, 1 H) 7.10 (t, *J*=8.72 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.52 (d, *J*=1.77 Hz, 1 H) 8.02 (s, 1 H) 8.17 (s, 3 H) 8.88 (d, *J*=8.59 Hz, 1 H).

Example 155



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (200 mg, 0.90 mmol) [Prepared according to the procedure of Example 151], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-

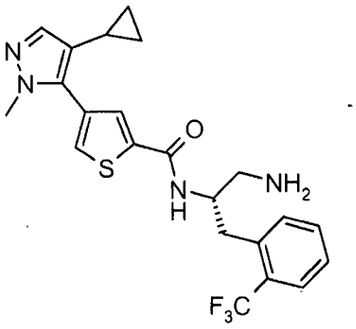
isoindole-1,3(2H)-dione (291 mg, 0.87 mmol) [Prepared according to the procedure of preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (512 mg, 1.09 mmol) in Chloroform (9 mL). DIEA (790 µL, 4.52 mmol) was added and the mixture stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (250 mg, 50%): LC-MS (ES) m/z = 503 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (250 mg, 0.45 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (400 µL). Hydrazine (66 µL, 2.10 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH). The compound was further purified on reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) affording the TFA salt which was neutralized on silica (90:10:1 $CHCl_3$/MeOH/NH_4OH).

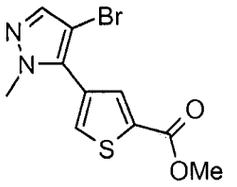
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (142 mg, 0.31 mmol, 70%): LC-MS (ES) m/z = 373 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.92 - 3.04 (m, 4 H) 3.79 (s, 3 H) 4.30 -4.43 (m, 1 H) 6.36 (d, *J*=1.77 Hz, 1 H) 7.02 (td, *J*=8.53, 2.15 Hz, 1 H) 7.13 (t, *J*=7.83 Hz, 2 H) 7.26 - 7.35 (m, 1 H) 7.52 (d, *J*=2.02 Hz, 1 H) 8.04 (s, 1 H) 8.19 (s, 3 H) 8.93 (d, *J*=8.34 Hz, 1 H).

Example 156



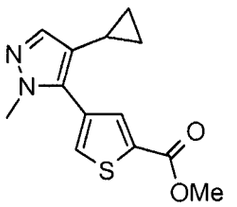
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



NBS (747 mg, 4.20 mmol) was added in portions to a 50 mL sealed tube reactor containing methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (860 mg, 3.48 mmol) [prepared according to the procedure of Example 37] in Tetrahydrofuran (THF) (17 mL) at room temperature. The mixture was heated to 70 °C for 1.5 hours, cooled to room temperature and partitioned between $CHCl_3$ and H_2O. The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (20 - 40% EtOAc / hexanes) affording the title compound (867 mg, 83%): LC-MS (ES) m/z = 303 $(M+H)^+$.

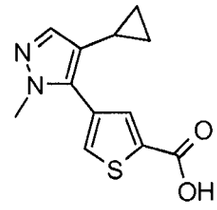
b) methyl 4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 20 mL sealed tube reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (505 mg, 1.68 mmol), cyclopropylboronic acid (447 mg, 5.20 mmol), Cesium Carbonate (1.90 g, 5.84 mmol) and $PdCl_2$(dppf)-CH_2Cl_2Adduct (43.6 mg, 0.05 mmol) in Tetrahydrofuran (THF) (8.5 mL). The

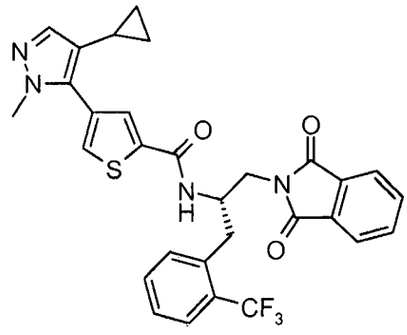
reaction was heated to 70 °C for 1.5 hours, cooled and partitioned between $CHCl_3$ and H_2O. The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (20 - 40% EtOAc / Hexane) affording the title compound (0.42 g, 1.60 mmol, 95%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) 4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (0.42 g, 1.60 mmol) in Tetrahydrofuran (THF) (8 ml). 6N NaOH (8 ml, 48.0 mmol) was added slowly and the reaction stirred at 70 °C overnight. The reaction was cooled and partitioned between $CHCl_3$ and H_2O. The pH of the aqueous layer was adjusted to ~ 3 by the addition of 6N HCl. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed affording the title compound (0.42 g, 1.60 mmol, 95%) which was used without further purification: LC-MS (ES) m/z = 249 $(M+H)^+$.

d) 4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (105 mg, 0.42 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (152 mg, 0.39 mmol) [prepared according to Preparation 6] and PyBrop (246 mg, 0.52 mmol) in Chloroform (6 mL). DIEA (370 µL, 2.19 mmol) was added and the mixture stirred overnight at room temperature. The mixture was adsorbed onto silica and purified

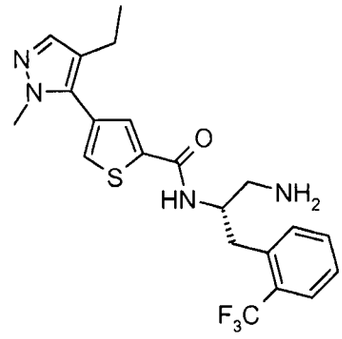
via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (171 mg, 66%): LC-MS (ES) m/z = 579 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (102 mg, 0.18 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (2 mL). Hydrazine (40 µL, 1.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

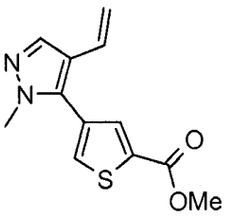
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (65 mg, 0.12 mmol, 66 % yield): LC-MS (ES) m/z = 449 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.45 - 0.54 (m, 2 H) 0.76 - 0.83 (m, 2 H) 1.62 - 1.71 (m, 1 H) 3.03 - 3.21 (m, 4 H) 3.82 (s, 3 H) 4.46 - 4.56 (m, 1 H) 7.21 (s, 1 H) 7.42 (t, *J*=7.45 Hz, 1 H) 7.53 (t, *J*=7.45 Hz, 1 H) 7.66 (dd, *J*=19.96, 7.58 Hz, 2 H) 7.95 (d, *J*=1.26 Hz, 1 H) 8.18 (s, 3 H) 8.24 (d, *J*=1.26 Hz, 1 H) 9.11 (d, *J*=9.09 Hz, 1 H).

Example 157



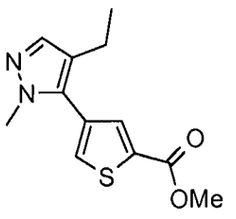
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 4-(4-ethenyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



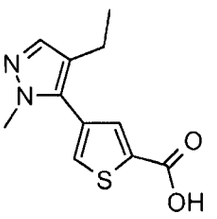
To a 5 mL sealed tube reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (473 mg, 1.57 mmol) [prepared according to the procedure of Example 156], pyridine - triethenylboroxine (1:1) (666 mg, 2.77 mmol), $Pd(PtBu_3)_2$ (16.8 mg, 0.03 mmol) and Cs_2CO_3 (1.72 g, 5.28 mmol) in 1,4-Dioxane (6.3 mL) and water (1.6 mL). The reaction was heated at 70 °C for 2 hours and partitioned between $CHCl_3$ (75 mL) / H_2O (75 mL). The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (25-70% EtOAc/Hexane) affording the desired product: LC-MS (ES) m/z = 249 $(M+H)^+$.

b) methyl 4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



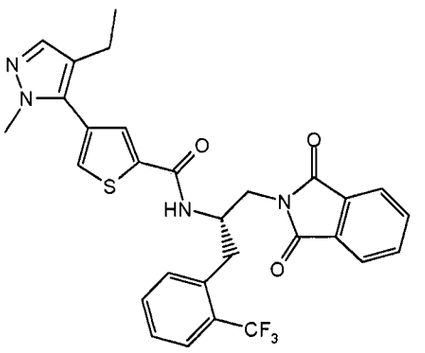
To a 100 mL round-bottomed flask was added methyl 4-(4-ethenyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate and 10% Pd/C in ethyl acetate (15 mL). The mixture was evacuated slightly, refilled with H_2 from a balloon and stirred vigorously under an atmosphere of H_2 for 1 hour. The reaction was filtered through a 0.2 µm PTFE membrane filter and used without further purification (153 mg, 0.60 mmol, 87%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) 4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (192 mg, 0.77 mmol) in Tetrahydrofuran (THF) (4 mL). 6N NaOH (4 mL, 24.0 mmol) was added slowly, the reaction stirred at 70 °C overnight. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer adjusted to pH 3 by the addition of 6N HCl. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed affording the title compound (181 mg, quant.) used without further purification: LC-MS (ES) m/z = 237 $(M+H)^+$.

d) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (106 mg, 0.45 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (164 mg, 0.43 mmol) [prepared according to Preparation 6] and PyBrop (254 mg, 0.54 mmol) in Chloroform (6 mL). DIEA (400 µL, 2.29 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (182 mg, 0.32 mmol, 71%): LC-MS (ES) m/z = 567 $(M+H)^+$.

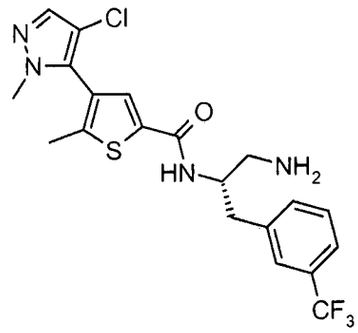
e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (101 mg, 0.18 mmol) in

Tetrahydrofuran (THF) (5 mL) and Methanol (2 mL). Hydrazine (40 µL, 1.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

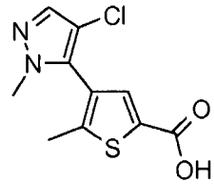
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (65 mg, 0.12 mmol, 68%): LC-MS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=7.45 Hz, 3 H) 2.44 (q, *J*=7.41 Hz, 2 H) 2.94 - 3.17 (m, 4 H) 3.80 (s, 3 H) 4.41 - 4.57 (m, 1 H) 7.37 - 7.45 (m, 2 H) 7.53 (t, *J*=7.45 Hz, 1 H) 7.66 (dd, *J*=19.96, 7.58 Hz, 2 H) 7.88 (d, *J*=1.01 Hz, 1 H) 8.16 (s, 4 H) 9.10 (d, *J*=8.84 Hz, 1 H).

Example 158



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

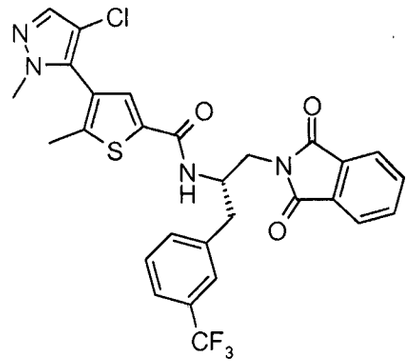
a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



NCS (1.355 g, 10.15 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.0 g, 8.46 mmol) [prepared according to the procedure of Preparation 10] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture

was heated to 70 °C for 2h. 6N NaOH (28 ml, 168 mmol) was added and the mixture stirred at 70 °C for an additional 2h. The mixture was cooled to room temperature and partitioned between $CHCl_3$ and H_2O. The pH of the aqueous layer was adjusted to ~ 3 by the addition of 6N HCl. The aqueous phase was washed several times with DCM and the combined organic fractions were dried with Na_2SO_4 and concentrated affording the title compound (2.36 g, 9.19 mmol, quant.): LC-MS (ES) m/z = 257 $(M+H)^+$.

b) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



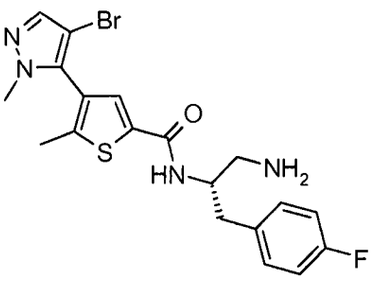
To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (181 mg, 0.70 mmol), 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (250 mg, 0.65 mmol) [Prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (399 mg, 0.85 mmol) in chloroform (8 mL). DIEA (620 µL, 3.55 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (319 mg, 0.50 mmol, 71%): LC-MS (ES) m/z = 587 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (319 mg, 0.50 mmol) in Tetrahydrofuran (THF) (4.9 mL) and Methanol (0.5 mL). Hydrazine (119 µL, 3.79 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

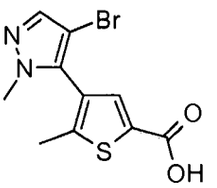
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (204 mg, 0.39 mmol, 79%): LC-MS (ES) m/z = 457 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.95 - 3.10 (m, 4 H) 3.71 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.49 - 7.61 (m, 3 H) 7.66 (s, 1 H) 7.69 (s, 1 H) 7.94 (s, 1 H) 8.16 (s, 3 H) 8.90 (s, 1 H).

Example 159



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

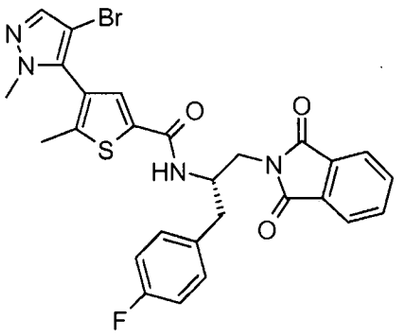
a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



NBS (1.84 g, 10.33 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2 g, 8.46 mmol) [prepared according to the procedure of Preparation 10] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture

was heated to 70 °C for 1h. 6N NaOH (28 ml, 168 mmol) was then added and the mixture stirred at 70 °C for 2h. The mixture was partitioned between $CHCl_3$ and H_2O and the aqueous layer was made acidic with 6N HCl. The aqueous phase was washed several times with $CHCl_3$ and the organic fractions were combined, dried over Na_2SO_4 and concentrated affording the title compound (2.68 g, 8.9mmol, quant.): LC-MS (ES) m/z = 302 $(M+H)^+$.

b) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (256 mg, 0.85 mmol), 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (1272 mg, 3.80 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (485 mg, 1.03 mmol) in Chloroform (8.5 mL). DIEA (750 µL, 4.29 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (319 mg, 0.50 mmol, 71%): LC-MS (ES) m/z = 583 $(M+H)^+$.

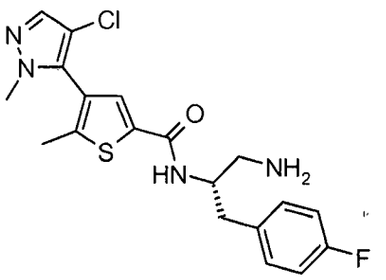
c) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (133 mg, 0.21 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (50 µL, 1.59

mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

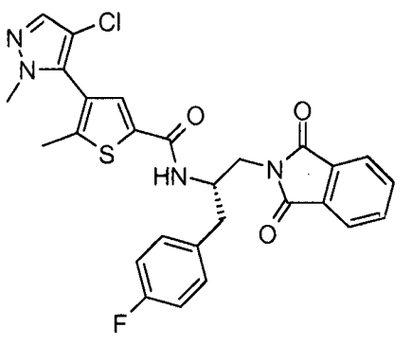
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (90 mg, 0.17 mmole, 83%): LC-MS (ES) m/z = 453 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.82 - 3.08 (m, 4 H) 3.72 (s, 3 H) 4.24 - 4.39 (m, 1 H) 7.11 (t, *J*=8.84 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.69 (s, 1 H) 7.89 (s, 1 H) 8.03 - 8.25 (m, 3 H) 8.73 - 8.90 (m, 1 H).

Example 160



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (276 mg, 1.08 mmol) [Prepared according to the procedure of Example 158], 2-[(2S)-2-amino-3-(4-

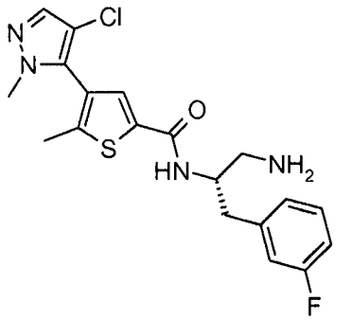
fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (317 mg, 0.95 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (612 mg, 1.31 mmol) in Chloroform (14 mL). DIEA (940 µL, 5.38 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (319 mg, 0.50 mmol, 71%): LC-MS (ES) m/z = 537 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (145 mg, 0.25 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (60 µL, 1.91 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

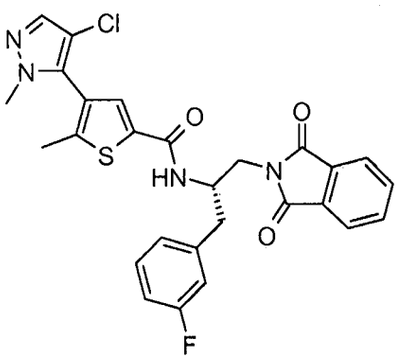
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (88 mg, 0.19 mmol, 77%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.81 - 3.10 (m, 4 H) 3.72 (s, 3 H) 4.25 - 4.40 (m, 1 H) 7.10 (t, *J*=8.84 Hz, 2 H) 7.31 (dd, *J*=8.21, 5.68 Hz, 2 H) 7.69 (s, 1 H) 7.94 (s, 1 H) 8.15 (s, 3 H) 8.85 (s, 1 H).

Example 161



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



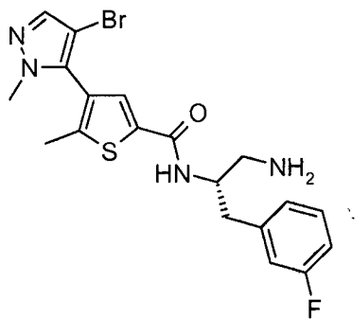
To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (187 mg, 0.73 mmol) [prepared according to the procedure of Example 158], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (233 mg, 0.70 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (412 mg, 0.88 mmol) in Chloroform (9 mL). DIEA (640 µL, 3.66 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (180 mg, 0.30 mmol, 42%): LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (186 mg, 0.31 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (76 µL, 2.42 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

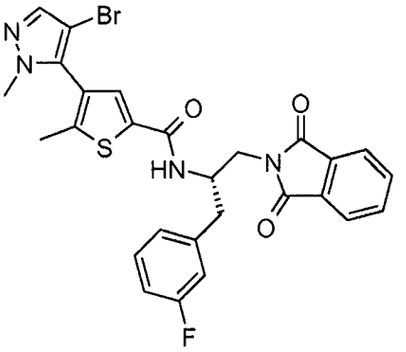
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (108 mg, 0.231, 74%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.91 - 3.03 (m, 4 H) 3.71 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.02 (td, *J*=8.59, 2.02 Hz, 1 H) 7.13 (t, *J*=7.07 Hz, 2 H) 7.26 - 7.36 (m, 1 H) 7.69 (s, 1 H) 7.95 (s, 1 H) 8.15 (s, 3 H) 8.88 (d, *J*=6.32 Hz, 1 H).

Example 162



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (191 mg, 0.63 mmol) [prepared according to the procedure of Example 159], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (209 mg, 0.62 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (359 mg, 0.77 mmol) in chloroform (7 mL). DIEA (560 µL, 3.21 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (171 mg, 0.29 mmol, 46%): LC-MS (ES) m/z = 583 $(M+H)^+$.

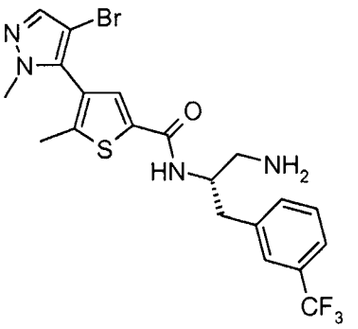
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (171 mg, 0.29 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (66 µL, 2.10 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified by column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (123 mg, 0.26 mmol, 88%): LC-MS (ES) m/z = 453 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.33 (s, 3 H) 2.91 - 3.03 (m, 4 H) 3.72 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.02

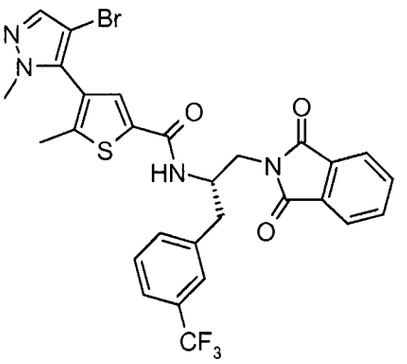
(td, *J*=8.46, 2.02 Hz, 1 H) 7.12 (d, *J*=7.33 Hz, 2 H) 7.27 - 7.35 (m, 1 H) 7.64 - 7.71 (m, 1 H) 7.92 (s, 1 H) 8.14 (s, 3 H) 8.79 - 8.93 (m, 1 H).

Example 163



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (180 mg, 0.60 mmol) [prepared according to the procedure of Example 159], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (203 mg, 0.58 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (340 mg, 0.72 mmol) in Chloroform (6 mL). DIEA (530 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was

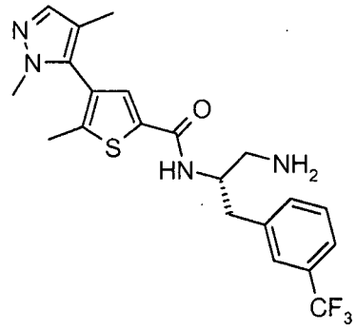
adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (259 mg, 0.41 mmol, 69%): LC-MS (ES) m/z = 633 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (259 mg, 0.41 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (90 µL, 2.87 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

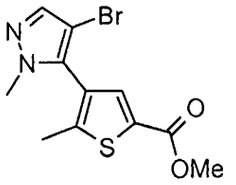
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (172 mg, 0.33 mmol, 80%): LC-MS (ES) m/z = 503 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H) 3.03 (d, *J*=6.06 Hz, 4 H) 3.71 (d, *J*=5.81 Hz, 3 H) 4.31 - 4.41 (m, 1 H) 7.49 - 7.56 (m, 2 H) 7.60 (d, *J*=6.82 Hz, 1 H) 7.64 - 7.71 (m, 2 H) 7.93 (d, *J*=12.88 Hz, 1 H) 8.18 (s, 3 H) 8.88 - 8.99 (m, 1 H).

Example 164



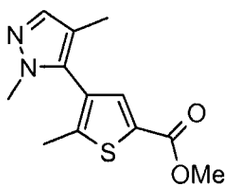
Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



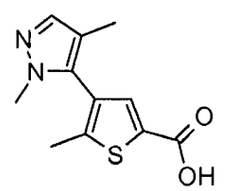
NBS (2.03 g, 11.41 mmol) was added in portions to a 75 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.1 g, 8.89 mmol) [prepared according to the procedure of Preparation 10] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture was heated to 70 °C for 1 hour. The reaction mixture was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4, the reaction mixture adsorbed onto silica and purified via column chromatography (15 - 40% EtOAc/Hex) affording the title compound (2.57 g, 8.15 mmol, 92%): LC-MS (ES) m/z = 316 $(M+H)^+$.

b) methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate



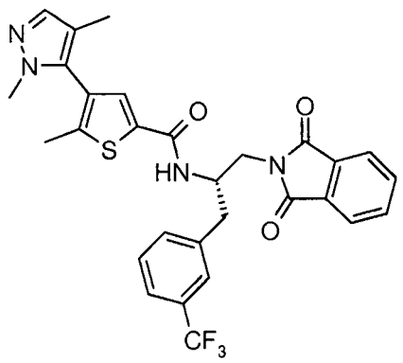
To a 350 mL sealed flask reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (2.57 g, 8.15 mmol), trimethylboroxine (2.27 ml, 16.31 mmol), K_2CO_3 (3.47 g, 25.1 mmol) and $Pd(dppf)Cl_2$ (426 mg, 0.83 mmol) in N,N-Dimethylformamide (DMF) (41 ml). The reaction was heated at 110 °C for 1 hour. The mixture was partitioned between $CHCl_3$ / H_2O, organic layer separated and dried with Na_2SO_4. The resulting material was adsorbed onto silica and purified via column chromatography (0-15% EtOAc/Hexane) affording the title compound (1.3 g, 4.76 mmol, 58%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylate (1.31 g, 5.23 mmol) in Tetrahydrofuran (THF) (25 mL). 6N NaOH (30 mL, 180 mmol) was added slowly and the reaction stirred at 70 °C overnight. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer adjusted to pH 3 by the addition of 6N HCl . The layers were separated, the organic layer was dried with Na_2SO_4 and the solvent was removed affording the title compound (1.3 g, 5.5 mmol, quant.) which was used without further purification: LC-MS (ES) m/z = 237 $(M+H)^+$.

d) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide



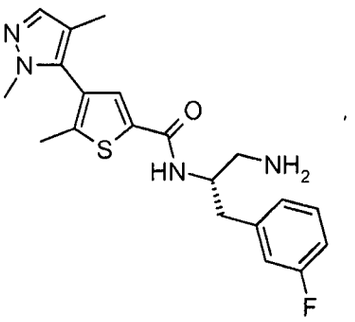
To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (170 mg, 0.68 mmol), 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (256 mg, 0.67 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (387 mg, 0.83 mmol) in chloroform (7 mL). DIEA (600 µL, 3.44 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (311 mg, 0.55 mmol, 80%): LC-MS (ES) m/z = 567 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-thiophenecarboxamide (311 mg, 0.55 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1.4 mL). Hydrazine (122 µL, 3.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

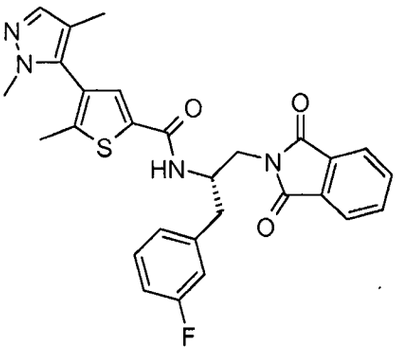
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (234 mg, 0.44 mmol, 79%): LC-MS (ES) m/z = 437 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.87 (s, 3 H) 2.26 (s, 3 H) 3.03 (d, *J*=6.82 Hz, 4 H) 3.62 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.38 (s, 1 H) 7.49 - 7.56 (m, 2 H) 7.58 - 7.61 (m, 1 H) 7.65 (s, 1 H) 7.87 (s, 1 H) 8.20 (s, 3 H) 8.89 (d, *J*=8.59 Hz, 1 H).

Example 165



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (207 mg, 0.83 mmol) [prepared according to the procedure of Example 164], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (279 mg, 0.83 mmol) [Prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (469 mg, 1.00 mmol) in chloroform (8 mL). DIEA (730 µL, 4.18 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (209 mg, 0.36 mmol, 43%): LC-MS (ES) m/z = 517 $(M+H)^+$.

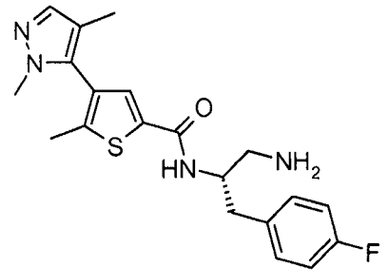
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (201 mg, 0.39 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (86 µL, 2.74 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (163 mg, 0.34 mmol, 87%): LC-MS (ES) m/z = 387 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 2.27 (s, 3 H) 2.87 - 3.09 (m, 4 H) 3.17 3.63 (s, 3 H) 4.28 -

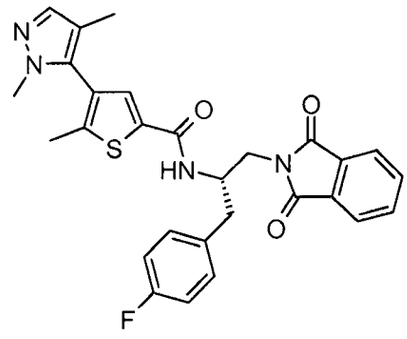
4.45 (m, 1 H) 6.97 - 7.06 (m, 1 H) 7.13 (t, *J*=7.20 Hz, 2 H) 7.27 - 7.35 (m, 1 H) 7.38 (s, 1 H) 7.89 (s, 1 H) 8.20 (s, 3 H) 8.88 (d, *J*=7.58 Hz, 1 H).

Example 166



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



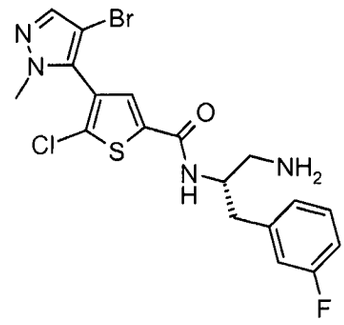
To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (253 mg, 1.02 mmol) [prepared according to the procedure of Example 164], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (335 mg, 1.00 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (574 mg, 1.23 mmol) in chloroform (10 mL). DIEA (930 µL, 5.32 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (132 mg, 0.25 mmol, 24%): LC-MS (ES) m/z = 517 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (132 mg, 0.26 mmol) in Tetrahydrofuran (THF) (2 mL) and Methanol (1 mL). Hydrazine (57 µL, 1.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (95:5:0.5 $CHCl_3$/MeOH/NH_4OH).

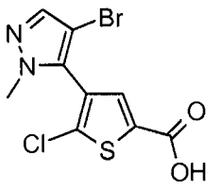
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (104 mg, 0.22 mmol, 84%): LC-MS (ES) m/z = 387 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 2.27 (s, 3 H) 2.84 - 3.11 (m, 4 H) 3.63 (s, 3 H) 4.24 - 4.39 (m, 1 H) 7.10 (t, *J*=8.72 Hz, 2 H) 7.31 (dd, *J*=8.21, 5.68 Hz, 2 H) 7.38 (s, 1 H) 7.87 (s, 1 H) 8.18 (s, 3 H) 8.83 (s, 1 H).

Example 167



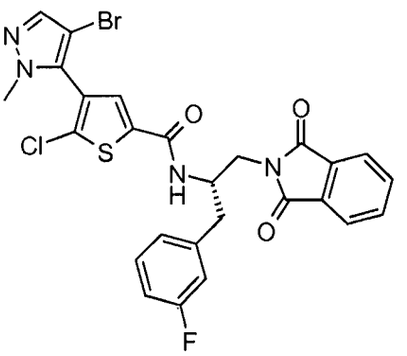
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid



NBS (1.243 g, 6.98 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1.47 g, 5.73 mmol) [Prepared according to the procedure of Example 151] in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture was heated to 70 °C for 1h. 6N NaOH (20 ml, 120 mmol) was then added and the mixture stirred at 70 °C for an additional 2h. The mixture was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4 and concentrated affording the title compound which was used without further purification (385 mg, 1.4 mmol, 30%): LC-MS (ES) m/z = 302 $(M+H)^+$.

b) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



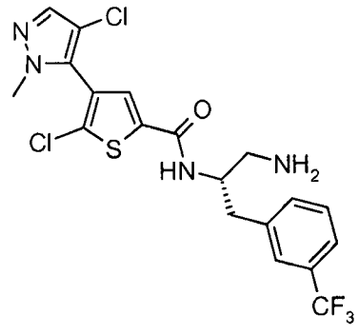
To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (204 mg, 0.60 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (215 mg, 0.64 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.7 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (380 mg, 0.81 mmol) in chloroform (6 mL). DIEA (570 µL, 3.26 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (247 mg, 45%): LC-MS (ES) m/z = 603 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (133 mg, 0.22 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1.2 mL). Hydrazine (50 µL, 1.59 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

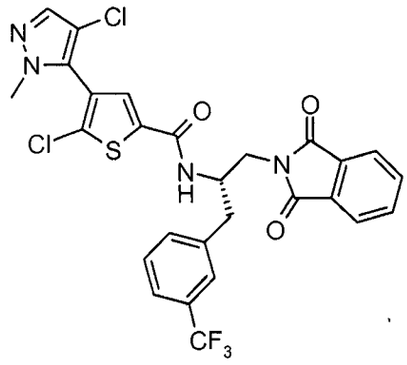
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (145 mg, 0.30 mmol, 66 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.91 - 3.03 (m, 4 H) 3.77 (s, 3 H) 4.30 - 4.41 (m, 1 H) 7.04 (td, *J*=8.53, 2.15 Hz, 1 H) 7.12 (d, *J*=7.07 Hz, 2 H) 7.28 - 7.36 (m, 1 H) 7.74 (s, 1 H) 8.02 - 8.14 (m, 4 H) 9.06 (s, 1 H).

Example 168



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (264 mg, 0.95 mmol) [prepared according to the procedure of Example 96], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (306 mg, 0.80 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (450 mg, 0.96 mmol) in chloroform (7 mL). DIEA (660 µl, 3.78 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (303 mg, 0.44 mmol, 56%): LC-MS (ES) m/z = 607 $(M+H)^+$.

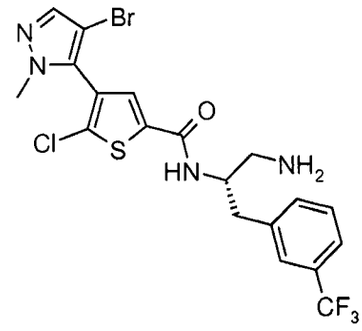
b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (303 mg, 0.50 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1.5 mL). Hydrazine (120 µL, 3.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (177 mg, 0.31 mmol, 61 % yield): LC-MS (ES) m/z = 479 $(M+H)^+$, ^1H NMR (400 MHz,

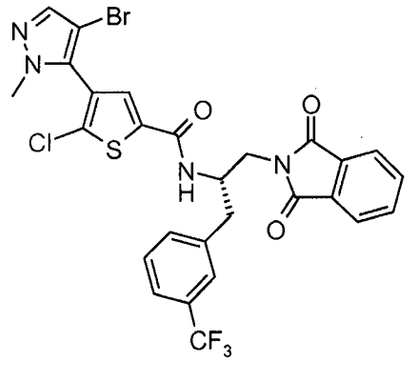
DMSO-d_6) δ ppm 2.97 - 3.08 (m, 4 H) 3.76 (s, 3 H) 4.28 - 4.44 (m, 1 H) 7.50 - 7.61 (m, 3 H) 7.66 (s, 1 H) 7.71 - 7.75 (m, 1 H) 8.10 (s, 4 H) 9.16 (d, *J*=8.59 Hz, 1 H).

Example 169



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (183 mg, 0.54 mmol) [prepared according to the procedure of Example 167], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (201 mg, 0.52 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (298 mg, 0.64 mmol) in chloroform (5 mL). DIEA (470 µL, 2.69 mmol) was

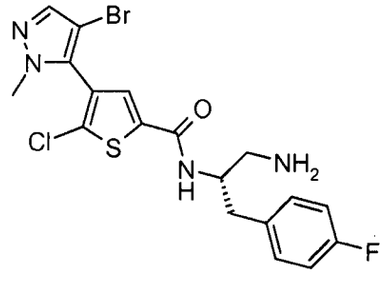
added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (246 mg, 0.36 mmol, 69%): LC-MS (ES) m/z = 653 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (246 mg, 0.38 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (0.083 mL, 2.64 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

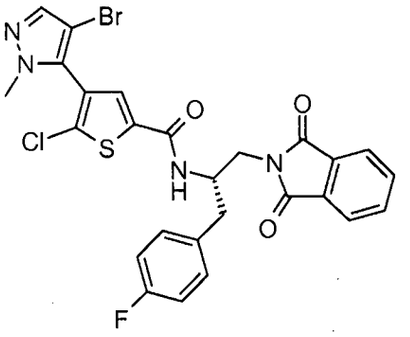
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (134 mg, 0.22 mmol, 57 % yield): LC-MS (ES) m/z = 523 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.04 (d, *J*=4.55 Hz, 4 H) 3.76 (s, 3 H) 4.29 - 443 (m, 1 H) 7.50 - 7.61 (m, 3 H) 7.66 (s, 1 H) 7.70 - 7.75 (m, 1 H) 8.06 - 8.18 (m, 4 H) 9.17 (s, 1 H).

Example 170



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (340 mg, 1.00 mmol) [prepared according to the procedure of Example 167], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (374 mg, 1.12 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (626 mg, 1.34 mmol) in chloroform (10 mL). DIEA (980 µL, 5.61 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (229 mg, 0.35 mmol, 31%): LC-MS (ES) m/z = 603 $(M+H)^+$.

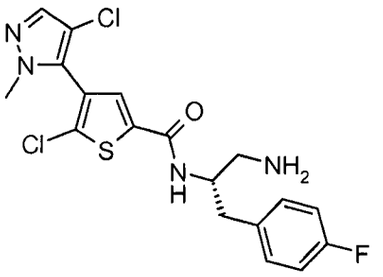
b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (229 mg, 0.38 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1.2 mL). Hydrazine (90 µL, 2.87 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (99

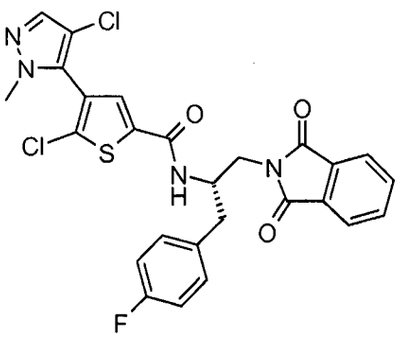
mg, 0.17 mmol, 45 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.90 (d, *J*=6.82 Hz, 2 H) 2.95 - 3.06 (m, 2 H) 3.77 (s, 3 H) 4.27 - 4.39 (m, 1 H) 7.11 (t, *J*=8.72 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.74 (s, 1 H) 8.01 - 8.21 (m, 4 H) 9.06 (s, 1 H).

Example 171



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (320 mg, 1.16 mmol) [prepared according to the procedure of Example 168], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (318 mg, 0.95 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (535 mg, 1.14 mmol) in Chloroform (9.5 mL). DIEA (840 µl, 4.81 mmol) was added

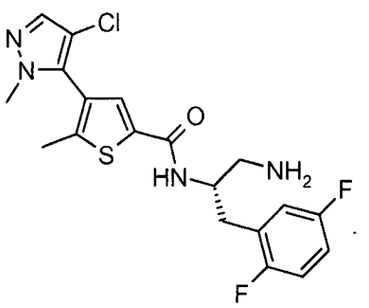
and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (106 mg, 0.16 mmol, 17%): LC-MS (ES) m/z = 557 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (106 mg, 0.19 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1.5 mL). Hydrazine (45 µL, 1.43 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

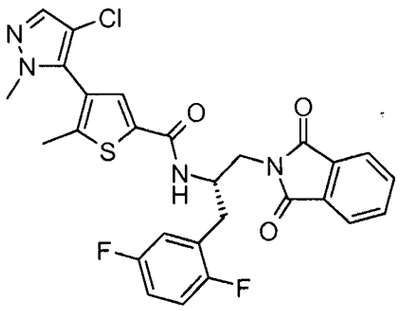
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (65 mg, 0.12 mmol, 65 % yield): LC-MS (ES) m/z = 429 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 - 3.10 (m, 4 H) 3.77 (s, 3 H) 4.27 - 4.38 (m, 1 H) 7.11 (t, *J*=8.72 Hz, 2 H) 7.26 - 7.35 (m, 2 H) 7.68 - 7.76 (m, 1 H) 8.10 (s, 4 H) 9.11 (d, *J*=7.33 Hz, 1 H).

Example 172



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (219 mg, 0.85 mmol) [prepared according to the procedure of Example 158], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (290 mg, 0.82 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (481 mg, 1.03 mmol) in chloroform (8.5 mL). DIEA (750 µL, 4.29 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (246 mg, 0.44 mmol, 52%): LC-MS (ES) m/z = 555 $(M+H)^+$.

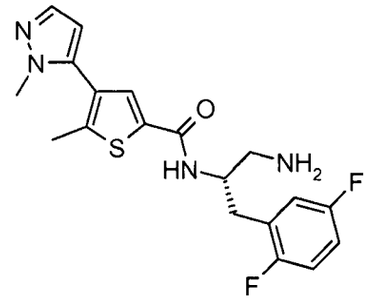
b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-thiophenecarboxamide (246 mg, 0.44 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (100 µL, 3.19 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (147 mg, 0.28 mmol, 64 % yield): LC-MS (ES) m/z = 425 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.34 (s, 3 H) 2.93 - 3.07 (m, 4 H) 3.71 (s, 3 H) 4.34 - 4.50 (m, 1 H)

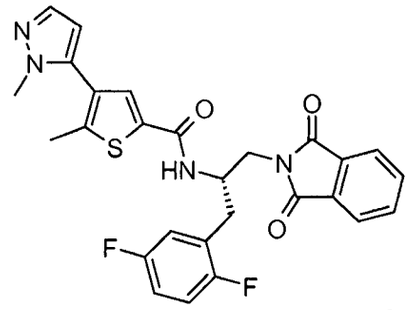
7.04 - 7.14 (m, 1 H) 7.19 (td, *J*=9.03, 4.67 Hz, 2 H) 7.69 (s, 1 H) 7.93 (s, 1 H) 8.14 (s, 3 H) 8.87 (d, *J*=8.59 Hz, 1 H).

Example 173



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



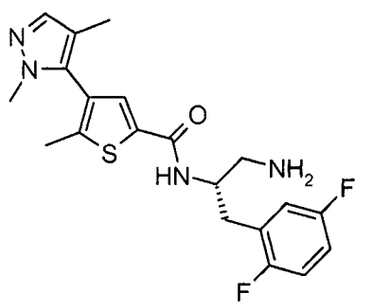
To a 50 mL round-bottomed flask was added 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (171 mg, 0.77 mmol) [prepared according to the procedure of Example 151], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (270 mg, 0.77 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (436 mg, 0.93 mmol) in chloroform (7.5 mL). DIEA (680 µL, 3.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (246 mg, 0.44 mmol, 52%): LC-MS (ES) m/z = 521 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (243 mg, 0.47 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (0.103 mL, 3.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

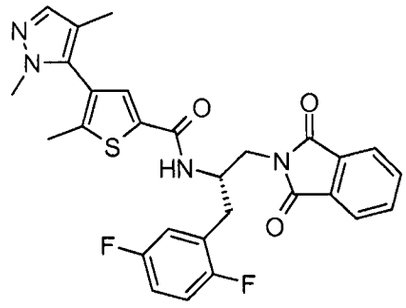
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (132 mg, 0.27 mmol, 58 % yield): LC-MS (ES) m/z = 391 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H) 2.87 - 3.10 (m, 4 H) 3.78 (s, 3 H) 4.36 - 4.47 (m, 1 H) 6.35 (d, *J*=1.77 Hz, 1 H) 7.05 - 7.13 (m, 1 H) 7.16 - 7.28 (m, 2 H) 7.52 (d, *J*=1.52 Hz, 1 H) 8.00 (s, 1 H) 8.16 (s, 3 H) 8.88 (d, *J*=8.59 Hz, 1 H).

Example 174



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) *N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide



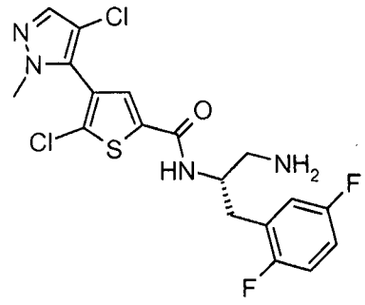
To a 50 mL round-bottomed flask was added 4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxylic acid (208 mg, 0.88 mmol) [prepared according to the procedure of Example 164], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (288 mg, 0.82 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (503 mg, 1.07 mmol) in Chloroform (8.5 mL). DIEA (770 µL, 4.41 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (292 mg, 0.55 mmol, 62%): LC-MS (ES) m/z = 535 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide (292 mg, 0.55 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (1 mL) Hydrazine (120 µL, 3.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

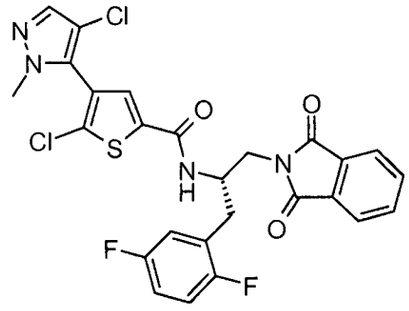
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (163 mg, 0.32 mmol, 59 % yield): LC-MS (ES) m/z = 405 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 (s, 3 H) 2.27 (s, 3 H) 2.94 - 3.06 (m, 4 H) 3.63 (s, 3 H) 4.35 - 4.49 (m, 1 H) 7.05 - 7.12 (m, 1 H) 7.16 - 7.27 (m, 2 H) 7.38 (s, 1 H) 7.86 (s, 1 H) 8.16 (s, 3 H) 8.83 (d, *J*=8.84 Hz, 1 H).

Example 175



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



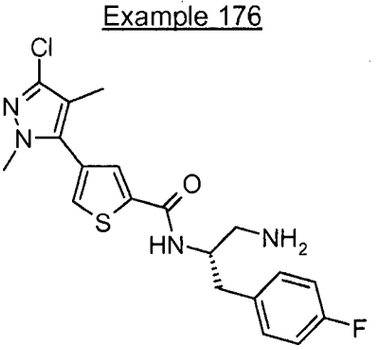
To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (235 mg, 0.85 mmol) [prepared according to the procedure of Example 96], 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (290 mg, 0.82 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (479 mg, 1.02 mmol) in chloroform (8.5 mL). DIEA (742 µL, 4.25 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (174 mg, 0.30 mmol, 36%): LC-MS (ES) m/z = 575 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (174 mg, 0.30 mmol) in Tetrahydrofuran (THF) (3.6 mL) and Methanol (1 mL). Hydrazine (70 µL, 2.23 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

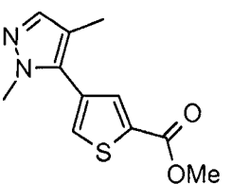
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (115 mg, 0.21 mmol, 70 % yield): LC-MS (ES) m/z = 445 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 3.09 (m, 4 H) 3.76 (s, 3 H) 4.33 - 4.48 (m, 1 H) 7.06 - 7.15 (m, 1 H) 7.20 (td, *J*=9.09, 4.55 Hz, 2 H) 7.74 (s, 1 H) 8.10 (s, 1 H) 8.13 (s, 3 H) 9.14 (d, *J*=8.84 Hz, 1 H).

Example 176



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

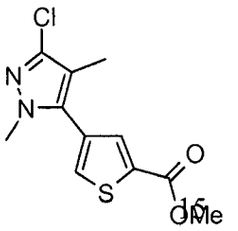
a) methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a 350 mL sealed flask reactor was added methyl 4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (3.45 g, 11.46 mmol) [prepared according

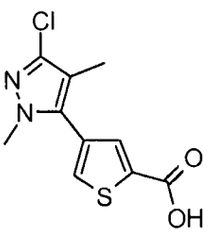
to the procedure of Example 156], trimethylboroxine (2.7 ml, 19.40 mmol), K_2CO_3 (4.75 g, 34.4 mmol) and $Pd(dppf)Cl_2$ (599 mg, 1.17 mmol) in N,N-Dimethylformamide (DMF) (57 mL). The reaction was heated at 110 °C for 1 hour, cooled to room temperature and partitioned between $CHCl_3$ / H_2O. The organic layer was separated, dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (0-30%EtOAc/Hexane) affording the title compound (2.07 g, 8.76 mmol, 76%): LC-MS (ES) m/z = 251 $(M+H)^+$.

b) methyl 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



NCS (1.78 g, 13.09 mmol) was added in portions to a 125 mL sealed tube reactor containing methyl 4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.07 g, 8.76 mmol) in Tetrahydrofuran (THF) (40 ml) at room temperature. The mixture was heated to 100 °C for 1 hour. Upon completion the product was partitioned between $CHCl_3$ and H_2O, the organic layer dried with Na_2SO_4, solvents removed by vacuum distillation affording the title compound (2.18 g, 7.97 mmol, 91%) which was used without further purification: LC-MS (ES) m/z = 271 $(M+H)^+$.

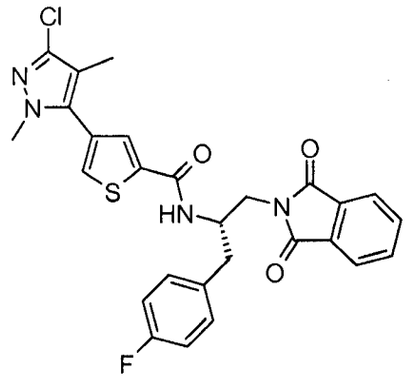
c) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (2.15 g, 7.94 mmol) in Tetrahydrofuran (THF) (30 ml). 6N NaOH (30 mL, 180 mmol) was added slowly and the reaction stirred at 70 °C overnight. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer

adjusted to ~ 3 by the addition of 6N HCl. The layers were separated, the organic layer dried with Na_2SO_4 and solvent removed affording the title compound (1.35 g, 5.26 mmol, 66%) which was used in the next step without further purification LC-MS (ES) m/z = 257 $(M+H)^+$.

d) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (294 mg, 1.14 mmol), 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (409 mg, 1.22 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (645 mg, 1.38 mmol) in chloroform (10 mL). DIEA (1 mL, 5.73 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (534 mg, 0.92 mmol, 81%): LC-MS (ES) m/z = 537 $(M+H)^+$.

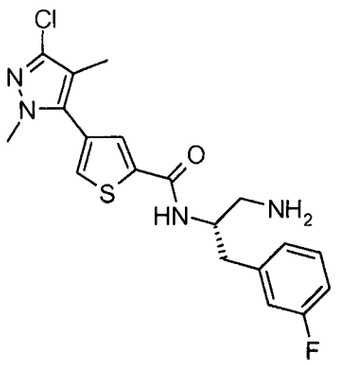
c) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (534 mg, 0.994 mmol) in Tetrahydrofuran (THF) (9 mL) and Methanol (1 mL). Hydrazine (220 µL, 7.01 mmol) was added and the reaction stirred overnight at room temperature. The

reaction mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

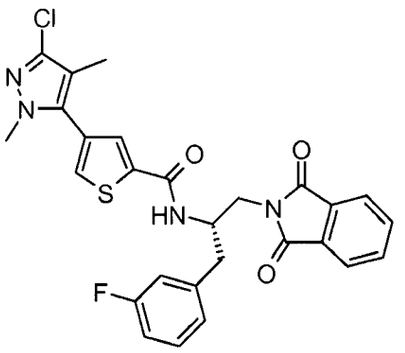
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (354 mg, 0.70 mmol, 70 % yield): LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (s, 3 H) 2.91 - 3.02 (m, 4 H) 3.79 (s, 3 H) 4.30 - 4.41 (m, 1 H) 7.10 (t, *J*=8.84 Hz, 2 H) 7.27 - 7.36 (m, 2 H) 8.01 (d, *J*=1.26 Hz, 1 H) 8.15 (s, 3 H) 8.21 (d, *J*=1.26 Hz, 1 H) 9.04 (d, *J*=8.34 Hz, 1 H).

Example 177



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



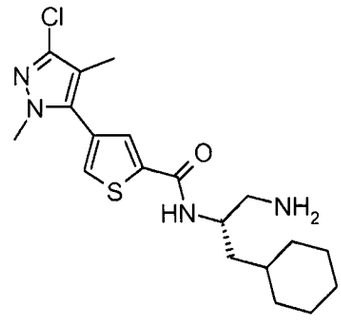
To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (291 mg, 1.13 mmol) [prepared according to the procedure of Example 176], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (409 mg, 1.22 mmol) [prepared according to the procedure of Preparation 6 except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (654 mg, 1.39 mmol) in chloroform (10 mL). DIEA (1 mL, 5.73 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (427 mg, 0.76 mmol, 67%): LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (427 mg, 0.79 mmol) in Tetrahydrofuran (THF) (7.5 mL) and Methanol (1 mL). Hydrazine (175 µL, 5.58 mmol) was added and the solution stirred at 25 °C overnight. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

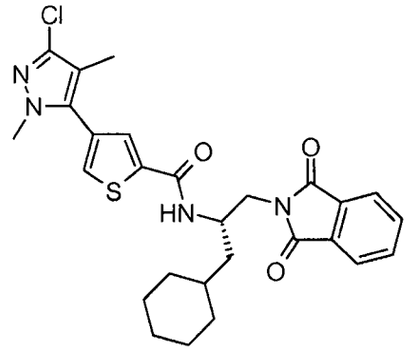
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (296 mg, 0.59 mmol, 74 % yield): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.99 (s, 3 H) 2.95 - 3.06 (m, 4 H) 3.79 (s, 3 H) 4.33 - 4.45 (m, 1 H) 7.02 (td, *J*=8.59, 2.02 Hz, 1 H) 7.09 - 7.18 (m, 2 H) 7.26 - 7.36 (m, 1 H) 8.01 (d, *J*=1.01 Hz, 1 H) 8.16 (s, 3 H) 8.22 (s, 1 H) 9.07 (d, *J*=8.34 Hz, 1 H).

Example 178



Preparation of *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (150 mg, 0.58 mmol) [prepared according to the procedure of Example 176], 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (176 mg, 0.54 mmol) [prepared according to the procedure of Preparation 6, except substituting 3-cyclohexyl-N-{[(1,1-dimethylethyl)oxy]carbonyl}-L-alanine (5g, 18.4 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (336 mg, 0.72 mmol) in chloroform (6 mL). DIEA (520 µL, 2.98 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (336 mg, 0.61 mmol, quant.): LC-MS (ES) m/z = 526 $(M+H)^+$.

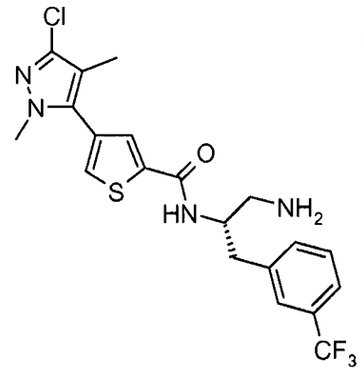
b) *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

348

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-{(1S)-2-cyclohexyl-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (366 mg, 0.697 mmol) in Tetrahydrofuran (THF) (6.5 mL) and Methanol (1 mL). Hydrazine (155 µL, 4.94 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

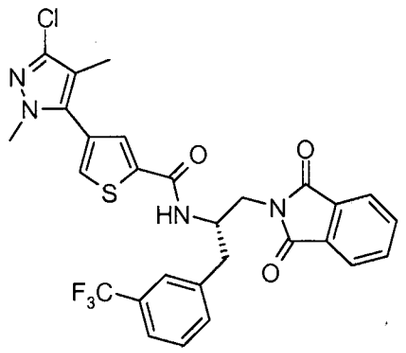
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (173 mg, 0.35 mmol, 50 % yield): LC-MS (ES) m/z = 395 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 0.80 - 0.92 (m, 1 H) 0.92 - 1.01 (m, 1 H) 1.13 (d, *J*=6.57 Hz, 2 H) 1.22 (d, *J*=12.88 Hz, 1 H) 1.29 (s, 1 H) 1.32 - 1.43 (m, 1 H) 1.48 - 1.56 (m, 1 H) 1.58 (d, *J*=5.05 Hz, 1 H) 1.63 (s, 3 H) 1.73 - 1.84 (m, 1 H) 1.99 (s, 3 H) 2.94 (d, *J*=5.31 Hz, 2 H) 3.78 (s, 3 H) 4.22 - 4.36 (m, 1 H) 8.03 (s, 1 H) 8.05 (s, 3 H) 8.19 (s, 1 H) 8.80 (d, *J*=8.59 Hz, 1 H).

Example 179



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (238 mg, 0.93 mmol) [prepared according to the procedure of Example 176], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (355 mg, 0.92 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (5.0 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (532 mg, 1.13 mmol) in chloroform (9.5 mL). DIEA (820 µL, 4.70 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (448 mg, 0.72 mmol, 78%): LC-MS (ES) m/z = 587 $(M+H)^+$.

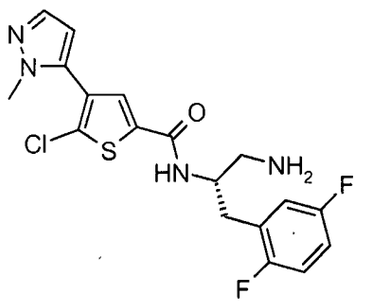
b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (468 mg, 0.80 mmol) in Tetrahydrofuran (THF) (7.5 mL) and Methanol (1 mL). Hydrazine (175 µL, 5.58 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (321 mg, 0.58 mmol, 72 % yield): LC-MS (ES) m/z = 457 $(M+H)^+$, ^1H NMR (400 MHz,

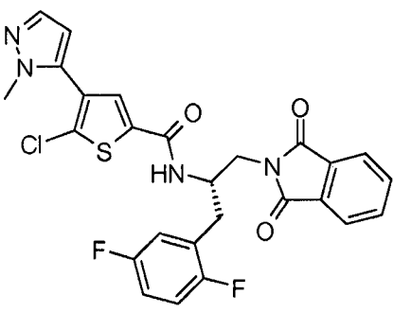
DMSO-d_6) δ ppm 1.98 (s, 3 H) 3.05 (d, *J*=7.07 Hz, 4 H) 3.77 (s, 3 H) 4.33 - 4.44 (m, 1 H) 7.49 - 7.57 (m, 2 H) 7.58 - 7.62 (m, 1 H) 7.66 (s, 1 H) 8.01 (d, *J*=1.26 Hz, 1 H) 8.11 (s, 3 H) 8.17 (d, *J*=1.26 Hz, 1 H) 9.02 (d, *J*=8.59 Hz, 1 H).

Example 180



Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-chloro-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (147 mg, 0.61 mmol), 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (216 mg, 0.61 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (341.4 mg, 0.73 mmol) in chloroform (6 mL). DIEA (530 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70%

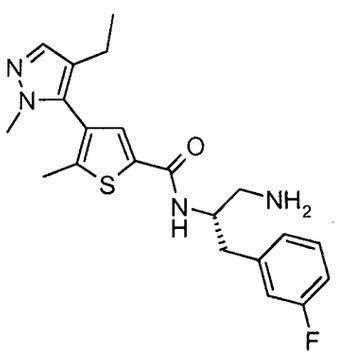
EtOAc/Hex) affording the title compound (233 mg, 0.43 mmol, 71%): LC-MS (ES) m/z = 541 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (233 mg, 0.43 mmol) in Tetrahydrofuran (THF) (5 mL) and Methanol (1 mL). Hydrazine (95 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (165 mg, 0.32 mmol, 75 % yield): LC-MS (ES) m/z = 411 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.88 - 3.14 (m, 4 H) 3.85 (s, 3 H) 4.37 - 4.50 (m, 1 H) 6.48 (d, *J*=1.77 Hz, 1 H) 7.09 (t, *J*=8.34 Hz, 1 H) 7.19 (dt, *J*=9.09, 4.55 Hz, 1 H) 7.29 (ddd, *J*=8.84, 5.68, 3.16 Hz, 1 H) 7.55 (d, *J*=1.52 Hz, 1 H) 8.22 (s, 3 H) 8.27 (s, 1 H) 9.32 (d, *J*=8.84 Hz, 1 H).

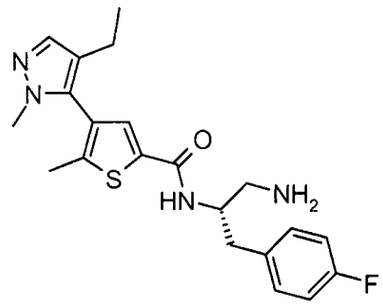
Example 181



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared according to the procedure of Example 109, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (184 mg, 0.55 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione [prepared according to Preparation 6]: LC-MS (ES) m/z = 401 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (t, *J*=7.33 Hz, 3 H) 2.13 - 2.33 (m, 5 H) 2.86 - 3.08 (m, 4 H) 3.60 (s, 3 H) 4.27 - 4.43 (m, 1 H) 6.96 - 7.07 (m, 1 H) 7.11 (d, *J*=6.32 Hz, 2 H) 7.30 (s, 1 H) 7.43 (s, 1 H) 7.85 (s, 1 H) 8.19 (s, 3 H) 8.85 (s, 1 H).

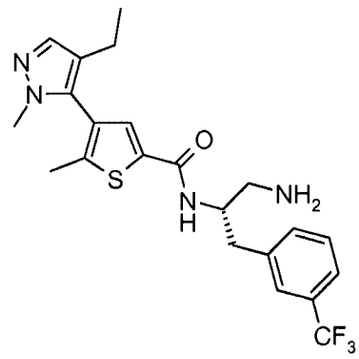
Example 182



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared according to the procedure of Example 109, except substituting 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (207 mg, 0.62 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione [prepared according to Preparation 6]: LC-MS (ES) m/z = 401 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (t, *J*=7.20 Hz, 3 H) 2.25 (s, 5 H) 2.88 - 3.00 (m, 4 H) 3.61 (s, 3 H) 4.25 - 4.40 (m, 1 H) 7.01 - 7.17 (m, 2 H) 7.26 - 7.35 (m, 2 H) 7.42 (s, 1 H) 7.82 (s, 1 H) 8.17 (s, 3 H) 8.81 (s, 1 H).

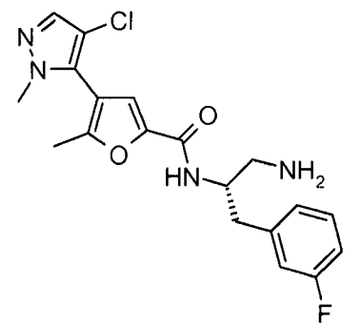
Example 183



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

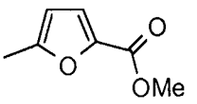
The title compound was prepared according to the procedure of Example 109, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (158 mg, 0.41 mmol) for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione [prepared according to Preparation 6]: LC-MS (ES) m/z = 451 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.04 (t, *J*=7.33 Hz, 3 H) 2.24 (s, 5 H) 3.03 (d, *J*=6.32 Hz, 4 H) 3.59 (s, 3 H) 4.35 (s, 1 H) 7.42 (s, 1 H) 7.46 - 7.57 (m, 2 H) 7.59 (d, *J*=6.57 Hz, 1 H) 7.64 (s, 1 H) 7.84 (s, 1 H) 8.20 (s, 3 H) 8.88 (s, 1 H).

Example 184



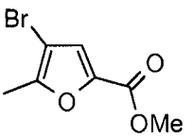
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) methyl 5-methyl-2-furancarboxylate



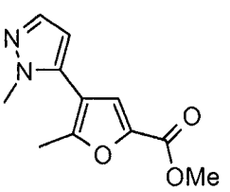
To a 200 mL round-bottomed flask with condenser was added 5-methyl-2-furancarboxylic acid (2.5 g, 19.82 mmol) in Methanol (100 mL). H_2SO_4 (10.5 mL, 197 mmol) was added slowly at room temperature. The reaction mixture was heated to 50 °C overnight. The reaction mixture was cooled to 0 °C and a saturated solution of $NaHCO_3$ was added to neutral pH followed by 5N NaOH to pH 10. $CHCl_3$ was added and the organic phase was separated, dried with Na_2SO_4 and concentrated affording the title compound (2.3 g, 16.3 mmol, 82%): LC-MS (ES) m/z = 141 $(M+H)^+$.

b) methyl 4-bromo-5-methyl-2-furancarboxylate



To a solution of methyl 5-methyl-2-furancarboxylate (2.33 g, 16.29 mmol) and aluminum chloride (3.3 g, 24.75 mmol) in chloroform (50 ml) at room temperature was added Br_2 (1.1 ml, 21.35 mmol). The resulting solution was stirred at room temperature in a 150 mL sealed tube reactor for 2 hours. Upon completion, the solution was cooled in an ice bath, H_2O added and reaction partitioned between $CHCl_3$ / H_2O. The organic layer was washed with $NaHCO_3$ and then $Na_2S_2O_3$. The organic layer was dried with Na_2SO_4, concentrated, adsorbed onto silica and purified via column chromatography (0-20% EtOAc/Hexanes) affording the title compound (2.13 g, 9.72 mmol, 60%): LC-MS (ES) m/z = 221 $(M+H)^+$.

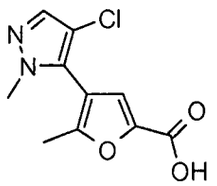
c) methyl 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



To a 5 mL sealed flask reactor was added methyl 4-bromo-5-methyl-2-furancarboxylate (1.13 g, 5.16 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.31 g, 6.30 mmol) [prepared according to the procedure of Preparation 7], K_3PO_4 (3.87 g, 18.23 mmol) and $Pd_2(dba)_3$ (153 mg,

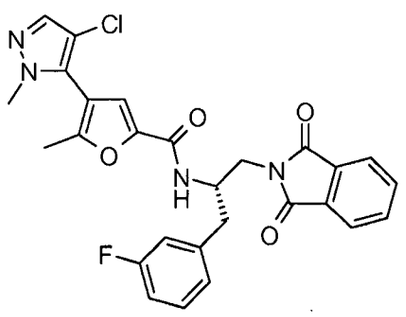
0.17 mmol) and $P(OMe)_3$ (32 µL, 0.27 mmol) in 1,4-Dioxane (23 mL). The reaction was heated at 95 °C for 4 hours, cooled to room temperature and partitioned between $CHCl_3$ / H2O. The organic layer was separated, dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (0-15%EtOAc/Hexanes) affording the title compound (967 mg, 4.39 mmol, 85%): LC-MS (ES) m/z = 271 $(M+H)^+$.

d) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



NCS (709 mg, 5.31 mmol) was added in portions to a 150 mL sealed tube reactor containing methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (967 mg, 4.39 mmol) in Tetrahydrofuran (THF) (20 mL) at room temperature. The mixture was heated to 70 °C for 1 hour. 6N NaOH (20 mL, 120 mmol) was then added and the mixture stirred at 70 °C for an additional 2h. The mixture was partitioned between $CHCl_3$ and H_2O and the pH of the aqueous phase was adjusted to ~3 with 6N HCl. The organic layer was separated, dried with Na_2SO_4 and concentrated affording the title compound (1.13 g, 4.41 mmol, quant.) which was used without further purification: LC-MS (ES) m/z = 241 $(M+H)^+$.

e) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (244 mg, 0.95 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (320 mg, 0.95 mmol)

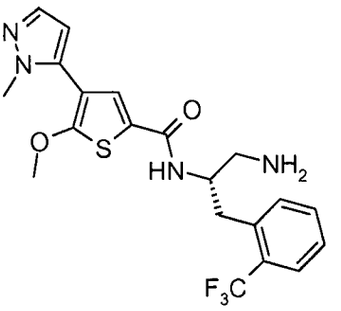
[prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.0 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (533 mg, 1.14 mmol) in chloroform (9 mL). DIEA (830 µL, 4.75 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (242 mg, 0.465 mmol, 49%): LC-MS (ES) m/z = 521 $(M+H)^+$.

f) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide (238 mg, 0.46 mmol) in Tetrahydrofuran (THF) (3.6 mL) and Methanol (1 mL). Hydrazine (100 µL, 3.19 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

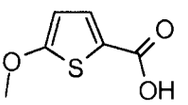
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (157 mg, 0.32 mmol, 71 % yield): LC-MS (ES) m/z = 391 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.31 (s, 3 H) 2.91 - 3.03 (m, 4 H) 3.73 (s, 3 H) 4.36 - 4.49 (m, 1 H) 7.03 (t, *J*=7.71 Hz, 1 H) 7.07 - 7.14 (m, 2 H) 7.29 - 7.37 (m, 1 H) 7.39 (s, 1 H) 7.67 (s, 1 H) 8.14 (s, 3 H) 8.65 (d, *J*=8.59 Hz, 1 H).

Example 185



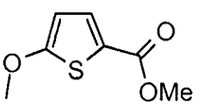
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 5-(methyloxy)-2-thiophenecarboxylic acid



2-(methyloxy)thiophene (1.01 g, 8.85 mmol) was added slowly over 15 min to a 100 mL round-bottomed flask containing 2.5M nBuLi in hexanes (3.8 mL, 9.50 mmol) in Tetrahydrofuran (THF) (40 mL) at -78 °C. After warming to room temperature and stirring for 2h, the mixture was cooled to -35 °C and crushed solid CO_2 was added. The mixture warmed to room temperature over 3 hours and was cooled in an ice bath and quenched with NH_4Cl(sat.). The cold reaction mixture was partitioned between $CHCl_3$ / H_2O, the aqueous layer was made acidic with 6N HCl. The separated organic layer was dried with Na_2SO_4 and concentrated affording the title compound (1.3 g, 8.05 mmol, 91%) which was used without further purification: LC-MS (ES) m/z = 159 $(M+H)^+$.

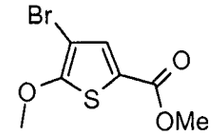
b) methyl 5-(methyloxy)-2-thiophenecarboxylate



To a 200 mL round-bottomed flask fitted with a condenser was added 5-(methyloxy)-2-thiophenecarboxylic acid (1.3 g, 8.22 mmol) in Methanol (40 mL). H_2SO_4 (5 mL, 94 mmol) was added slowly at room temperature and the reaction stirred at 50 °C overnight. The mixture was cooled to 0 °C and sat. $NaHCO_3$ was added to neutral pH followed by 5N NaOH to pH 10. The mixture was partitioned between H_2O / $CHCl_3$ and the organic phase was separated and dried over

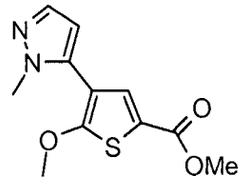
Na_2SO_4. The solution was adsorbed onto silica and purified via column chromatography (5-50% EtOAc/Hexanes) affording the title compound (827 mg, 4.56 mmol, 56%): LC-MS (ES) m/z = 173 $(M+H)^+$.

c) methyl 4-bromo-5-(methyloxy)-2-thiophenecarboxylate



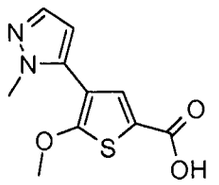
NBS (903 mg, 5.07 mmol) was added in portions to a 5 mL sealed tube reactor containing methyl 5-(methyloxy)-2-thiophenecarboxylate (0.73 g, 4.23 mmol) in N,N-Dimethylformamide (DMF) (20 mL) at room temperature and the reaction stirred for 1 hour. Additional NBS (249 mg) was added and after 1h at room temperature the product was partitioned between $CHCl_3$ and H_2O. The organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (0-25% EtOAc/Hexanes) affording the title compound (825 mg, 3.19 mmol, 75%): LC-MS (ES) m/z = 252 $(M+H)^+$.

d) methyl 5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



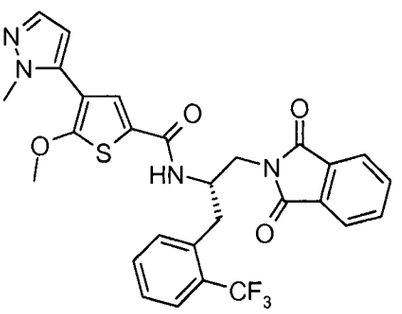
To a 350 mL sealed flask reactor was added methyl 4-bromo-5-(methyloxy)-2-thiophenecarboxylate (772 mg, 3.07 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (773 mg, 3.72 mmol) [prepared according to the procedure of Preparation 7], K_2CO_3 (1.419 g, 10.27 mmol) and $Pd(Pt\text{-}Bu_3)_2$ (103 mg, 0.20 mmol) in 1,4-Dioxane (12 mL) and Water (3 mL). The reaction was heated at 85 °C for 2 hours. The mixture was partitioned between $CHCl_3$ / H_2O and the aqueous layer made acidic with 6N HCl. The separated organic layer was dried over Na_2SO_4 and evaporated. The resulting material was adsorbed onto silica and purified via column chromatography (0-50%EtOAc/Hexane) affording the title compound (967 mg, 4.39 mmol, 85%): LC-MS (ES) m/z = 253 $(M+H)^+$.

e) 5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (203 mg, 0.805 mmol) in Tetrahydrofuran (THF) (4 mL). 6N NaOH (4 mL, 24.0 mmol) was added slowly, the reaction mixture stirred overnight at 70 °C. The mixture was neutralized by addition of 6N HCl and partitioned between $CHCl_3$ and H_2O. The layers were separated, the organic layer dried over Na_2SO_4 and concentrated affording the title compound (152 mg, 0.64 mmol, 79%), which was used in the next step without further purification: LC-MS (ES) m/z = 239 $(M+H)^+$.

f) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



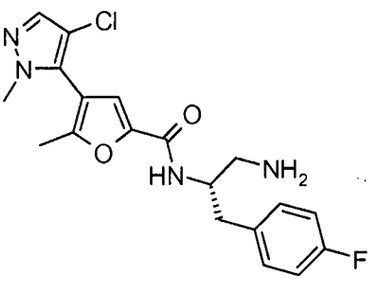
To a 50 mL round-bottomed flask was added 5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (148 mg, 0.62 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (242 mg, 0.63 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (356 mg, 0.76 mmol) in Chloroform (6 mL). DIEA (550 µL, 3.15 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (303 mg, 0.51 mmol, 82%): LC-MS (ES) m/z = 569 $(M+H)^+$.

g) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (303 mg, 0.51 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL) . Hydrazine (110 µL, 3.50 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

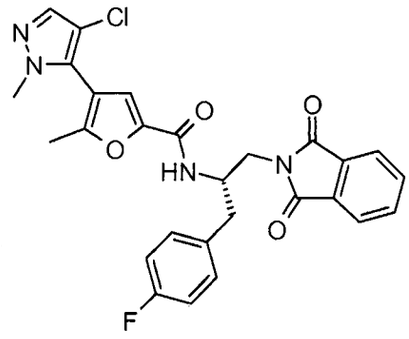
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (122 mg, 0.23 mmol, 45 % yield): LC-MS (ES) m/z = 439 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.93 - 3.02 (m, 1 H) 3.03 - 3.14 (m, 3 H) 3.82 (s, 3 H) 3.98 (s, 3 H) 4.41 - 4.53 (m, 1 H) 6.32 (s, 1 H) 7.38 - 7.49 (m, 2 H) 7.52 - 7.63 (m, 2 H) 7.68 (d, *J*=7.58 Hz, 1 H) 8.01 (s, 1 H) 8.17 (s, 3 H) 8.93 (d, *J*=8.84 Hz, 1 H).

Example 186



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (248 mg, 0.97 mmol) [prepared according to the procedure of Example 184], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (321 mg, 0.96 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (557 mg, 1.19 mmol) in chloroform (9.5 mL). DIEA (840 µL, 4.81 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (167 mg, 0.26 mmol, 67%): LC-MS (ES) m/z = 521 $(M+H)^+$.

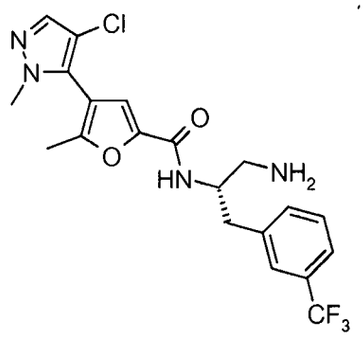
b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-2-furancarboxamide (144 mg, 0.27 mmol) in Tetrahydrofuran (THF) (2.5 mL) and Methanol (1 mL). Hydrazine (60 µL, 1.91 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (100 mg, 0.21 mmol, 74 % yield): LC-MS (ES) m/z = 391 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.31 (s, 3 H) 2.83 - 2.93 (m, 2 H) 2.94 - 3.04 (m, 2 H) 3.73 (s, 3 H)

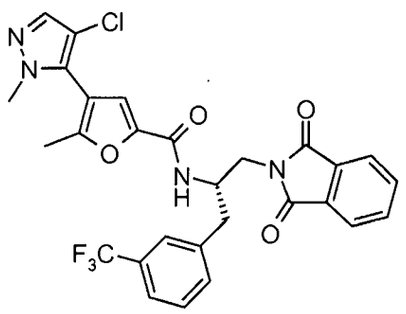
4.32 - 4.44 (m, 1 H) 7.12 (t, *J*=8.59 Hz, 2 H) 7.25 - 7.33 (m, 2 H) 7.35 (s, 1 H) 7.67 (s, 1 H) 8.07 (s, 3 H) 8.57 (d, *J*=8.59 Hz, 1 H).

Example 187



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (230 mg, 0.90 mmol) [prepared according to the procedure of Example 184], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (348 mg, 0.90 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (502 mg, 1.07 mmol) in chloroform (8.5 mL). DIEA (790 µL, 4.52 mmol) was added and the reaction stirred overnight at room temperature. The mixture

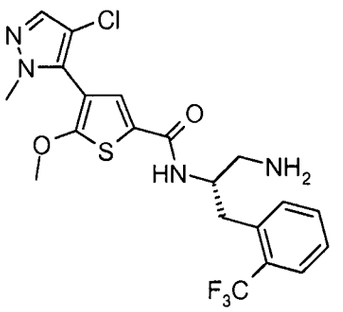
was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (247 mg, 0.43 mmol, 48%): LC-MS (ES) m/z = 571 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-2-furancarboxamide (247 mg, 0.433 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (95 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (206 mg, 0.38 mmol, 88 % yield): LC-MS (ES) m/z = 441 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.30 (s, 3 H) 2.97 - 3.08 (m, 4 H) 3.71 (s, 3 H) 4.35 - 4.49 (m, 1 H) 7.36 (s, 1 H) 7.54 (dt, *J*=19.20, 7.20 Hz, 3 H) 7.62 - 7.68 (m, 2 H) 8.14 (s, 3 H) 8.65 (d, *J*=8.84 Hz, 1 H).

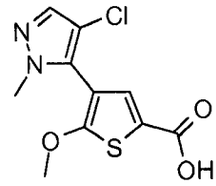
Example 188



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

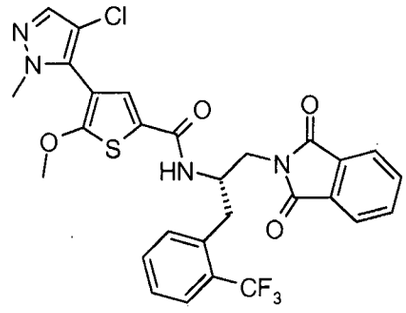
364

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid



NCS (382 mg, 2.80 mmol) was added in portions to a 50 mL sealed tube reactor containing methyl 5-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (642 mg, 2.54 mmol) [prepared according to the procedure of Example 185] in Tetrahydrofuran (THF) (12 mL) at room temperature. The mixture was heated to 70 °C for 1 hour. The reaction was cooled to room temperature, 6N NaOH (10 mL, 60.0 mmol) was added and the mixture stirred an additional 3h at 70 °C. The mixture was partitioned between $CHCl_3$ and H_2O and the aqueous layer was made acidic with 6N HCl. The organic layer was dried over Na_2SO_4 and concentrated affording the title compound (759 mg, 2.51 mmol, 98%) which was used without further purification: LC-MS (ES) m/z = 273 $(M+H)^+$.

b) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (85 mg, 0.31 mmol), 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (119 mg, 0.31 mmol) [prepared according to the procedure of Preparation 6] and PyBrop (180 mg, 0.384 mmol) in chloroform (3.5 mL). DIEA (270 µL, 1.54 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70%

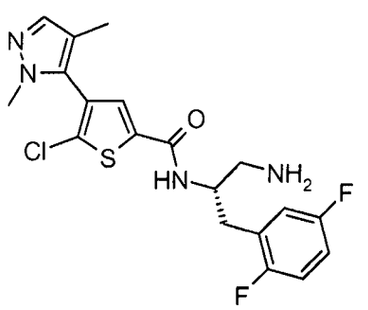
EtOAc/Hex) affording the title compound (94 mg, 0.14 mmol, 45%): LC-MS (ES) m/z = 603 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide (94 mg, 0.16 mmol) in Tetrahydrofuran (THF) (2 mL) and Methanol (1 mL). Hydrazine (35 µL, 1.12 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

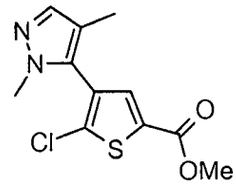
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (27 mg, 0.05 mmol, 31 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.93 - 3.14 (m, 4 H) 3.73 (s, 3 H) 4.00 (s, 3 H) 4.41 - 4.54 (m, 1 H) 7.43 (t, *J*=7.45 Hz, 1 H) 7.57 (ddd, *J*=14.59, 7.58, 7.39 Hz, 2 H) 7.62 - 7.65 (m, 1 H) 7.69 (d, *J*=7.83 Hz, 1 H) 7.82 - 7.89 (m, 1 H) 8.12 (s, 3 H) 8.80 (d, *J*=9.09 Hz, 1 H).

Example 189



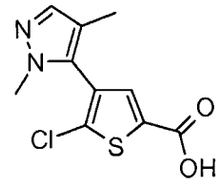
Preparation of *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



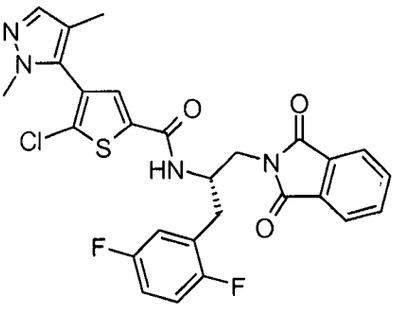
To a 350 mL sealed flask reactor was added methyl 4-bromo-5-chloro-2-thiophenecarboxylate (409 mg, 1.60 mmol) [prepared according to the procedure of Example 95], 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (388 mg, 1.75 mmol) [prepared according to the procedure of Preparation 17], K_2CO_3 (676 mg, 4.89 mmol) and $Pd(PtBu_3)_2$ (32 mg, 0.06 mmol) in 1,4-Dioxane (6 mL) and water (1.5 mL). The reaction was heated at 85 °C for 3 hours. The reaction was partitioned between $CHCl_3$ / H_2O and the pH of the aqueous layer was adjusted to ~3 with 6N HCl. The separated organic layer was dried with Na_2SO_4, adsorbed onto silica and purified via column chromatography (10-65% EtOAc/Hexanes) affording the title compound (106 mg, 0.39 mmol, %); LC-MS (ES) m/z = 271 $(M+H)^+$.

b) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a 100 mL round-bottomed flask was added methyl 5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (106 mg, 0.39 mmol) in Tetrahydrofuran (THF) (2 mL). 6N NaOH (2 mL, 12.00 mmol) was added slowly and the reaction mixture stirred overnight at 70 °C. The reaction was cooled to room temperature, partitioned between $CHCl_3$ and H_2O and the pH of the aqueous layer was adjusted to ~ 3 by the addition of 6N HCl. The layers were separated, the organic layer dried over Na_2SO_4 and concentrated affording the desired compound (96 mg, 0.37 mmol, 95%): LC-MS (ES) m/z = 257 $(M+H)^+$.

c) 5-chloro-*N*-{(1*S*)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (96 mg, 0.37 mmol), 2-[(2S)-2-amino-3-(2,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (125 mg, 0.40 mmol) [prepared according to the procedure of Preparation 18 except substituting 2,5-difluoro-L-phenylalanine (3.02 g, 15.0 mmol) for 2,6-difluoro-L-phenylalanine] and PyBrop (225 mg, 0.48 mmol) in chloroform (4 mL). DIEA (330 µL, 1.89 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (98 mg, 0.13 mmol, 34%): LC-MS (ES) m/z = 535 $(M+H)^+$.

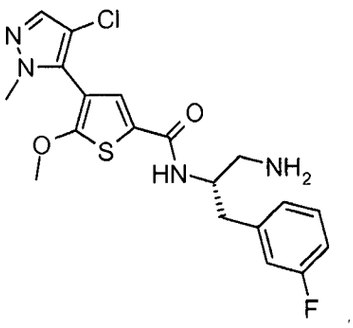
d) *N*-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 5-chloro-N-{(1S)-2-(2,5-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (98 mg, 0.18 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (40 µL, 1.27 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 CHCl3/MeOH/NH4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (52 mg, 0.10 mmol, 56 % yield): LC-MS (ES) m/z = 425 (M+H)+, ^{1}H NMR (400 MHz, DMSO-d6) δ ppm 1.94 (s, 3 H) 2.87 - 3.09 (m, 4 H) 3.69 (s, 3 H) 4.42 (d, J=6.32 Hz, 1 H) 7.10 (ddd, J=12.00, 8.34, 3.41 Hz, 1 H) 7.20 (td, J=9.16, 4.67 Hz, 1 H) 7.27

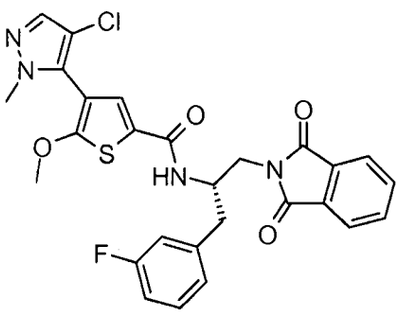
(ddd, J=8.97, 5.56, 3.16 Hz, 1 H) 7.39 (s, 1 H) 8.06 (s, 1 H) 8.13 (s, 3 H) 9.13 (d, J=8.84 Hz, 1 H).

Example 190



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (220 mg, 0.81 mmol) [prepared according to the procedure of Example 188], 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (281 mg, 0.84 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-fluoro-L-phenylalanine (5.03 g, 17.8 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (472 mg, 1.0 mmol) in Chloroform (8 mL). DIEA (710 µL, 4.07 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed

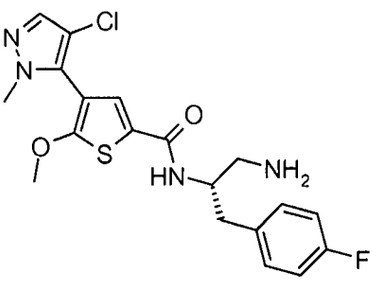
onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (281 mg, 0.51 mmol, 63%): LC-MS (ES) m/z = 553 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide (281 mg, 0.51 mmol) in Tetrahydrofuran (THF) (4.5 mL) and Methanol (1 mL). Hydrazine (120 µL, 3.82 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (145 mg, 0.28 mmol, 55 % yield): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.86 - 3.04 (m, 4 H) 3.71 (s, 3 H) 4.02 (s, 3 H) 4.31 - 4.41 (m, 1 H) 7.00 - 7.07 (m, 1 H) 7.11 (d, *J*=7.58 Hz, 2 H) 7.28 - 7.36 (m, 1 H) 7.64 (s, 1 H) 7.73 - 7.78 (m, 1 H) 7.98 (s, 3 H) 8.54 (s, 1 H).

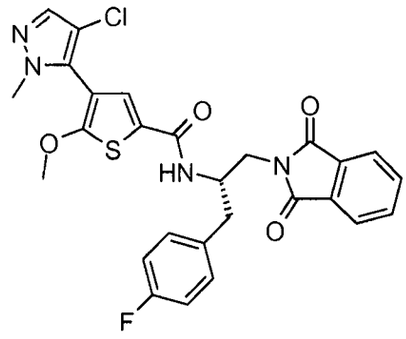
Example 191



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

370

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide



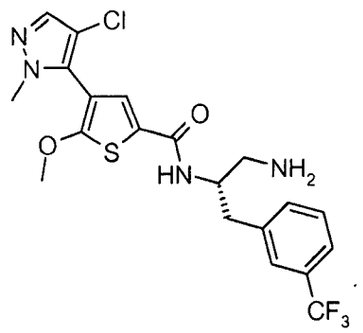
To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (208 mg, 0.76 mmol) [prepared according to the procedure of Example 188], 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (257 mg, 0.77 mmol) [prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-4-fluoro-L-phenylalanine (4.95 g, 17.5 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (435 mg, 0.93 mmol) in chloroform (7.6 mL). DIEA (670 µL, 3.84 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (238 mg, 0.43 mmol, 56%): LC-MS (ES) m/z = 553 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-(methyloxy)-2-thiophenecarboxamide (238 mg, 0.43 mmol) in Tetrahydrofuran (THF) (4 mL) and Methanol (1 mL). Hydrazine (95 µL, 3.03 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

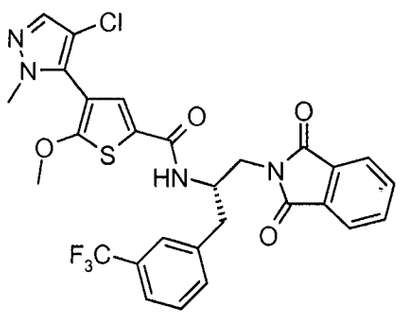
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (113 mg, 0.22 mmol, 50 % yield): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.82 - 2.92 (m, 2 H) 2.93 - 3.03 (m, 2 H) 3.71 (s, 3 H) 4.02 (s, 3 H) 4.26 - 4.37 (m, 1 H) 7.11 (t, *J*=8.46 Hz, 2 H) 7.26 - 7.32 (m, 2 H) 7.64 (s, 1 H) 7.69 - 7.84 (m, 1H) 7.95 (s, 3 H) 8.45 - 8.52 (m, 1H).

Example 192



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide



To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxylic acid (210 mg, 0.77 mmol) [prepared according to the procedure of Example 188], 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (294 mg, 0.764 mmol)

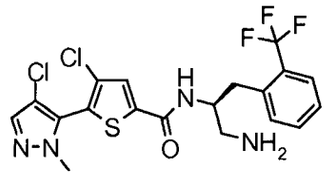
[prepared according to the procedure of Preparation 6, except substituting *N*-{[(1,1-dimethylethyl)oxy]carbonyl}-3-(trifluoromethyl)-L-phenylalanine (4.98 g, 15.0 mmol) for N-{[(1,1-dimethylethyl)oxy]carbonyl}-2-(trifluoromethyl)-L-phenylalanine] and PyBrop (442 mg, 0.94 mmol) in chloroform (7.6 mL). DIEA (670 µL, 3.84 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica and purified via column chromatography (25 - 70% EtOAc/Hex) affording the title compound (238 mg, 0.43 mmol, 56%): LC-MS (ES) m/z = 603 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide

To a 50 mL round-bottomed flask was added 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-2-thiophenecarboxamide (203 mg, 0.34 mmol) in Tetrahydrofuran (THF) (3 mL) and Methanol (1 mL). Hydrazine (80 µL, 2.55 mmol) was added and the reaction stirred overnight at room temperature. The mixture was adsorbed onto silica gel and purified via column chromatography (90:10:1 $CHCl_3$/MeOH/NH_4OH).

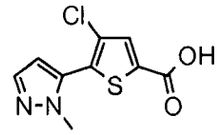
The neutral compound was dissolved in MeOH (2 mL), treated with excess 2M HCl in Et_2O and concentrated affording the HCl salt of the title compound (86 mg, 0.15 mmol, 44 % yield): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.92 - 3.08 (m, 4 H) 3.70 (s, 3 H) 4.01 (s, 3 H) 4.30 - 4.42 (m, 1 H) 7.50 - 7.60 (m, 3 H) 7.61 - 7.66 (m, 2 H) 7.73 - 7.81 (m, 1H) 8.00 (s, 3 H) 8.52 - 8.68 (m, 1H).

Example 193



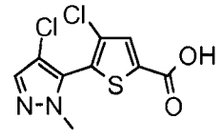
Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) 4-chloro-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of 5-bromo-4-chloro-2-thiophenecarboxylic acid (482 mg, 2 mmol) in dioxane/H_2O (4:1, 10 mL) was added 1,1'-bis(diphenylphosphino)ferrocenedichloro Palladium (II) dichloromethane complex (16.3 mg, 0.02 mmol), potassium carbonate (828 mg, 6 mmol) and 5-(5,5-dimethyl-1,3,2-dooxaborinan-2-yl)-1-methyl-1*H*-pyrazole (832 mg, 4 mmol)[prepared according to Preparation 7]. The reaction mixture was heated to 80 °C in a sealed tube for 20 hrs. The reaction mixture was poured into H_2O (100 mL) and extracted with DCM. The organic layer was dried over Na_2SO_4, concentrated and purified using silica (EtOAc / hexane (0 – 45% gradient)) affording the title compound as a white solid (401.7 mg, 83%): LC-MS (ES) m/z= 243 $(M+H)^+$.

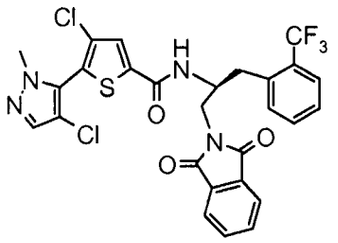
b) 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of 4-chloro-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (121 mg, 0.5 mmol) and N-chlorosuccinimide (67mg, 0.5 mmol) in THF (5 mL) was stirred in a sealed tube at 70 °C. After 4 hrs, the solution was concentrated and partitioned between DCM and H_2O. The aqueous layer was extracted several times with DCM. The organic fractions were combined, concentrated and azeotropically dried with toluene to give the title compound as a brown oil (136 mg, 98%): LC-MS (ES) m/z= 278 $(M+H)^+$.

c). 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide

374



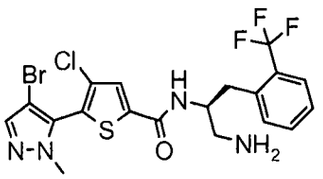
To a solution of 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (136.1 mg, 0.49 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (179 mg, 0.51 mmol)[prepared according to Preparation 6], diisopropylethyl amine (260 uL, 1.5 mmol) in DCM (5 mL) was added PyBrop (341 mg, 0.75 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, gradient 0- 50% ethyl acetate / hexane) affording the title compound (242 mg, 82%) as a white solid: LCMS (ES) m/z = 607 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (242 mg, 0.4 mmol) in THF-MeOH (1:1, 4 mL) was added hydrazine (75 uL, 2.42 mmol). After 12h, the solution was concentrated. The resulting residue was partitioned between DCM and H_2O. The organics were washed three times with water and acidified to pH ~ 1 with 6N aqueous HCl solution. The resulting mixture was extracted with water. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the desired product as a light yellow solid (77 mg, 40%): LCMS (ES) m/z 477 $(M+H)^+$, ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.08-3.11 (m, 4 H) 3.75 (s, 3 H) 4.50 (br. s., 1 H) 7.45 (t, *J*=6.95 Hz, 1H) 7.55 - 7.63 (m, 2H) 7.71 (d, *J*=7.83 Hz, 1 H) 7.78 (s, 1 H) 8.02 - 8.10 (m, 3 H) 8.12 (s, 1 H) 9.12 (d, *J*=9.09 Hz, 1 H)

375

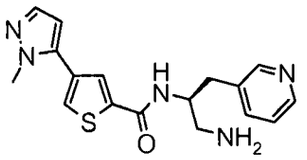
Example 194



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 193, except substituting N-bromosuccinimide (89 mg, 0.5 mmol) for and N-chlorosuccinimide: LCMS (ES) m/z 522 $(M+H)^+$, ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.0-3.13 (m, 4 H) 3.76 (s, 3 H) 4.50 (br. s., 1 H) 7.46 (d, *J*=7.58 Hz, 1 H) 7.55 - 7.66 (m, 2 H) 7.71 (d, *J*=7.83 Hz, 1 H) 7.78 (s, 1 H) 8.04 (br. s., 4 H).

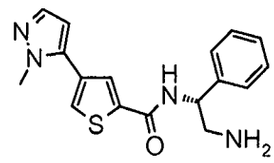
Example 195



Preparation of *N*-[(1*S*)-2-amino-1-(3-pyridinylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a light yellow solid according to the procedure of Example 6, except substituting 4-bromo-2-thiophenecarboxylic acid (62 mg, 0.3 mmol) for 5-bromo-2-thiophenecarboxylic acid and substituting 2-[(2*S*)-2-amino-3-(3-pyridinyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione -HCl (84 mg, 0.3 mmol)[prepared according to Preparation 19] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione-HCl: LC-MS (ES) m/z = 342 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.17 (dd, *J*=13.89, 10.86 Hz, 1 H) 3.33 - 3.36 (m, 2 H) 3.36 - 3.44 (m, 1 H) 3.96 (s, 3 H) 4.70 (dd, *J*=14.02, 6.19 Hz, 1 H) 6.47 (s, 1 H) 7.51 (s, 1 H) 7.88 (d, *J*=1.26 Hz, 1 H) 7.94 (s, 1 H) 8.02 (t, *J*=6.32 Hz, 1 H) 8.61 (d, *J*=7.83 Hz, 1 H) 8.76 (br. s., 1 H) 8.89 (br. s., 1 H).

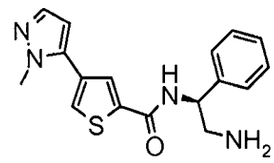
Example 196



Preparation of *N*-[(1*R*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (83 mg, 0.4 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl [(2*R*)-2-amino-2-phenylethyl]carbamate (94 mg, 0.4 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z = 327 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.44 (d, *J*=4.29 Hz, 1 H) 3.63 (br. s., 1 H) 4.18 (s, 3 H) 5.47 (dd, *J*=10.36, 4.55 Hz, 1 H) 6.88 (d, *J*=2.78 Hz, 1 H) 7.38 (d, *J*=7.07 Hz, 1 H) 7.44 (t, *J*=7.33 Hz, 2 H) 7.55 (d, *J*=7.83 Hz, 2 H) 8.08 (d, *J*=2.53 Hz, 1 H) 8.18 (d, *J*=1.26 Hz,1 H) 8.42 (d, *J*=1.26 Hz, 1 H).

Example 197



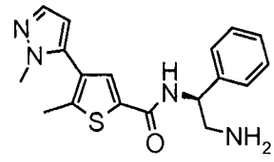
Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 20, except substituting 4-bromo-2-thiophenecarboxylic acid (83 mg, 0.4 mmol) for 4,5-dibromo-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate (94 mg, 0.4 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 327 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ

374

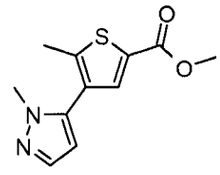
ppm 3.44 (d, J=2.78 Hz, 1 H) 3.60 (br. s., 1 H) 4.06 (br. s., 3 H) 5.47 (dd, J=10.36, 4.29 Hz, 1 H) 6.70 (br. s., 1 H) 7.38 (d, J=6.82 Hz, 1 H) 7.44 (t, J=7.20 Hz, 2 H) 7.53 (d, J=7.58 Hz, 2 H) 7.79 (br. s., 1 H) 8.04 (br. s.,1 H) 8.32 (br. s., 1 H).

Example 198



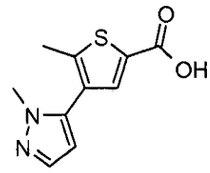
Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



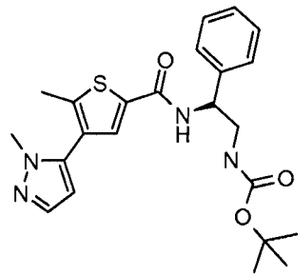
A solution of methyl 4-bromo-5-methyl-2-thiophenecarboxylate (2g, 8.51 mmol)[prepared in Preparation 10], potassium carbonate (5.88 g, 42.5 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.12 g, 10.21 mmol)[prepared according to Preparation 7] and bis(tri-t-butylphosphine)palladium(0) (0.22 g, 0.43 mmol) in 1,4-Dioxane (35 ml) and H_2O (7 ml) was stirred at 80 °C in a sealed tube for 1h. The reaction mixture was then partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 25% EtOAc in hexanes) affording methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate. This reaction was run in several batches (1g, 3 x 2g) which were combined for workup and purification affording the title compound (5.5 g, 78% combined yield) as a viscous yellow oil: LC-MS (ES) m/e 236 $(M+H)^+$.

b) 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (94 mg, 0.4 mmol) in 6N sodium hydroxide (0.67 ml, 4 mmol) and tetrahydrofuran (4 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~3 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the desired product (67 mg, 0.3 mmol, 75 % yield) as a yellow oil: LC-MS (ES) m/e 223 (M+H)+.

c) 1,1-dimethylethyl [(2S)-2-({[5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate



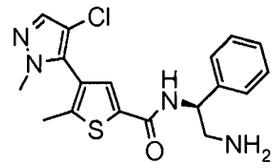
To a solution of 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (67 mg, 0.3 mmol), 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate (71 mg, 0.3 mmol) [prepared according to the procedure of Preparation 1] and diisopropylethylamine (0.16 ml, 0.9 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (210 mg, 0.45 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound (87 mg, 0.2 mmol, 65 % yield) as a yellow foam: LC-MS (ES) m/e 441 (M+H)+.

d). *N*-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (87 mg, 0.2 mmol) in DCM (2

mL) was added 4N HCl solution in dioxane (0.5 mL, 2 mmol) which stirred at ambient temperature for 15 h. The solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (26 mg, 0.06 mmol, 32%): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.49 (br. s., 3 H) 3.43 (d, *J*=4.80 Hz, 1 H) 3.55 (d, *J*=10.36 Hz, 1 H) 3.95 (s, 3 H) 5.41-5.43 (m, 1 H) 6.66 (d, *J*=2.27 Hz, 1 H) 7.38 (d, *J*=7.07 Hz, 1 H) 7.44 (t, *J*=7.33 Hz, 2 H) 7.48 - 7.53 (m, 2 H) 7.94 - 8.02 (m, 2 H).

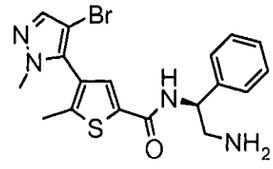
Example 199



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (89 mg, 0.4 mmol) [prepared according to Example 198] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid and substituting 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (94 mg, 0.4 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.38-2.41 (m, 1H), 3.38 (d, *J*=1.52 Hz, 1 H) 3.49 (d, *J*=10.86 Hz, 1 H) 3.73 (br. s., 3 H) 5.41 (d, *J*=3.54 Hz, 1 H) 7.30 - 7.50 (m, 5 H) 7.54 - 7.62 (m, 1 H) 7.81 (br. s., 1 H).

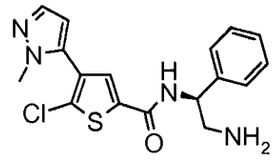
Example 200



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

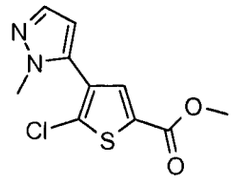
The title compound was prepared as a white solid according to the procedure of Example 24, except substituting 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (168 mg, 0.5 mmol) [prepared according to Example 198] for 4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid, N-bromosuccinimide (88.5 mg, 0.5 mmol) for N-chlorosuccinimide and 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate (71 mg, 0.3 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl (3-amino-4-phenylbutyl)carbamate: LC-MS (ES) m/z 341 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.39 (d, *J*=4.04 Hz, 3 H) 3.42 (br. s., 1 H) 3.55 (br. s., 1 H) 3.75-3.78 (m, 3 H) 5.45 (m, 1 H) 7.37 (d, *J*=7.07 Hz, 1 H) 7.40 - 7.46 (m, 2 H) 7.49 (br. s., 2 H) 7.59 - 7.68 (m, 1 H) 7.80 - 7.88 (m, 1 H).

Example 201



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

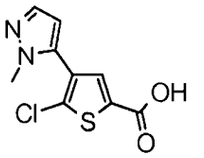
a) methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (2.56 g, 10.00 mmol)[prepared according to Example 95], 5-(5,5-dimethyl)-1,3,2-dioxaborinan-2-yl)-1-methyl-1H-pyrazole (3.88 g, 20.0 mmol)[prepared according to Preparation 7], potassium carbonate (4.15 g, 30.0 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.073 g, 0.1 mmol) in 1,4-Dioxane (12 mL) and water (3.00 mL) were heated at 80 °C in a sealed tube. After 3 hrs, another batch of 5-(5,5-dimethyl)-1,3,2-

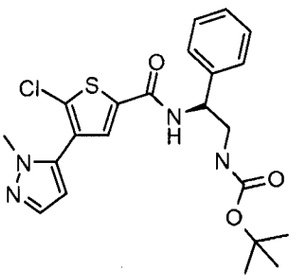
dioxaborinan-2-yl)-1-methyl-1H-pyrazole (1.94 g, 10.0 mmol) and 1,1'-bis(diphenylphosphino)ferrocenedichloro palladium (II) dichloromethane complex (0.073 g, 0.1 mmol) were added. After 2 hr, the mixture was concentrated and purified by silica gel eluting with 0-35% ethyl acetate / hexane affording the title compound as a yellow solid (1.74 g, 3.35 mmol, 34%): LC-MS (ES) m/z 257 $(M+H)^+$.

b) 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (304 mg, 1.18 mmol) in 6N sodium hydroxide (2 ml, 12 mmol) and Tetrahydrofuran (10 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~3 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the desired product (276 mg, 1.14 mmol, 96 % yield) as a yellow oil: LC-MS (ES) m/e 244 $(M+H)^+$.

c) 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate



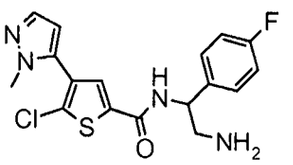
To a solution of 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (60 mg, 0.25 mmol), 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate (58 mg, 0.25 mmol) [prepared according to the procedure of Preparation 1] and diisopropylethylamine (0.12 ml, 0.75 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (190 mg, 0.41 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column

chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound (90 mg, 0.20 mmol, 79 % yield) as a colorless oil: LC-MS (ES) m/e 461 (M+H)+.

d). *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (90 mg, 0.20 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.5 mL, 2 mmol). After 15 h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (63 mg, 0.14 mmol, 74%): : LC-MS (ES) m/z 361 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.41 (dd, *J*=13.01, 4.17 Hz, 1 H) 3.63 (d, *J*=10.86 Hz, 1 H) 4.08 (s, 3 H) 5.45 (dd, *J*=10.48, 4.17 Hz, 1 H) 6.87 (d, *J*=2.27 Hz, 1 H) 7.36 (d, *J*=7.33 Hz, 1 H) 7.42 (t, *J*=7.33 Hz, 2 H) 7.54 (d, *J*=7.07 Hz, 2 H) 8.14 (d, *J*=2.27 Hz, 1 H) 8.27 (s, 1 H).

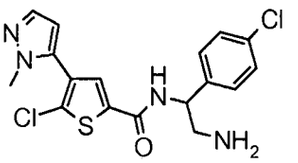
Example 202



Preparation of *N*-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate (63 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 379 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.40 (dd, *J*=13.01, 4.42 Hz, 1 H) 3.66 (d, *J*=2.02 Hz, 1 H) 4.03 - 4.15 (m, 3 H) 5.46 (dd, *J*=10.36, 4.29 Hz, 1 H) 6.84 (d, *J*=2.53 Hz, 1H) 7.15 (t, *J*=8.72 Hz, 2 H) 7.60 (dd, *J*=8.59, 5.05 Hz, 2 H) 8.10 (d, *J*=2.53 Hz, 1 H) 8.29 (s, 1 H).

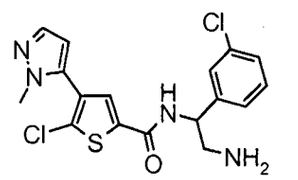
Example 203



Preparation of *N*-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(4-chlorophenyl)ethyl]carbamate (45 mg, 0.17 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 396 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.40 (d, *J*=4.55 Hz, 1 H) 3.58 (d, *J*=10.36 Hz, 1 H) 3.98 (s, 3 H) 5.41 (d, *J*=4.55 Hz, 1 H) 6.71 (s, 1 H) 7.43 (dt, *J*=4.74, 2.31 Hz, 2 H) 7.47 - 7.56 (m, 2 H) 7.92 (br. s., 1 H) 8.13 (s, 1 H).

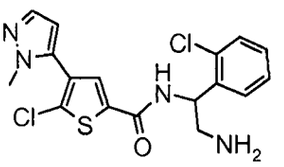
Example 204



Preparation of *N*-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(3-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 396 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ ppm 3.41 (dd, *J*=12.76, 4.93 Hz, 5 H) 3.36 - 3.47 (m, 3 H) 3.63 (s, 2 H) 3.59 (d, *J*=10.61 Hz, 6 H) 3.95 (s, 9 H) 4.02 (d, *J*=3.03 Hz, 15 H) 5.41 (dd, *J*=9.09, 3.79 Hz, 8 H) 6.67 (d, *J*=2.27 Hz, 3 H) 6.78 (br. s., 4 H) 7.33 - 7.49 (m, 23 H) 7.56 (br. s., 7 H) 8.06 (br. s., 8 H) 8.16 (d, *J*=16.93 Hz, 6 H).

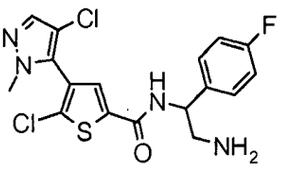
Example 205



Preparation of *N*-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

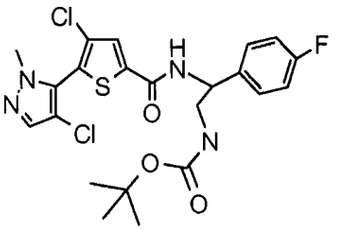
The title compound was prepared as a white solid according to the procedure of Example 201, except substituting 1,1-dimethylethyl [2-amino-2-(2-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [(2*S*)-2-amino-2-phenylethyl]carbamate: LC-MS (ES) m/z = 396 $(M+H)^+$, ^{1}H NMR (CD_3OD, 400 MHz) δ ppm 3.39 (br. s., 1 H) 3.56 (d, *J*=10.86 Hz, 1 H) 4.05 (d, *J*=3.03 Hz, 3 H) 5.87 (dd, *J*=10.74, 3.41 Hz, 1 H) 6.81 (br. s., 1 H) 7.39 (br. s., 2 H) 7.50 (d, *J*=6.57 Hz, 1 H) 7.70 (d, *J*=7.07 Hz, 1 H) 8.04 (br. s., 1 H) 8.26 (br. s., 1 H).

Example 206



Preparation of *N*-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [2-({[4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-(4-fluorophenyl)ethyl]carbamate

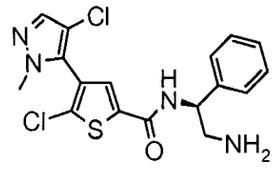


To a solution of 4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (67 mg, 0.24 mmol) [prepared according to Example 193], 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate (61 mg, 0.24 mmol) [prepared according to the procedure of Preparation 16], diisopropylethyl amine (126 uL, 0.72 mmol) in DCM (5 mL) was added PyBrop (168 mg, 0.36 mmol) in one portion. After 1h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, gradient 0- 50% ethyl acetate / hexane) affording the title compound (93 mg, 0.18 mmol, 76%) as a white solid: LCMS (ES) m/z = 514 $(M+H)^+$.

b). *N*-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [2-({[4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-2-(4-fluorophenyl)ethyl]carbamate (90 mg, 0.17 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.43 mL, 1.75 mmol). After 15h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (39.6 mg, 0.09 mmol, 52%): LC-MS (ES) m/z 414 $(M+H)^+$, ^{1}HNMR (400 MHz, MeOD) δ ppm 3.42 (d, *J*=2.78 Hz, 1 H) 3.56 (br. s., 1 H) 3.79 (s, 3 H) 5.43 (dd, *J*=10.23, 4.67 Hz, 1 H) 7.11 - 7.22 (m, 2 H) 7.49 - 7.57 (m, 2 H) 7.60 (s, 1 H) 7.93 (br. s., 1 H).

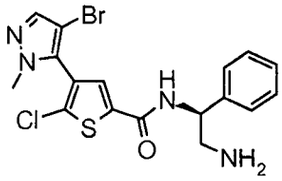
Example 207



Preparation of *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

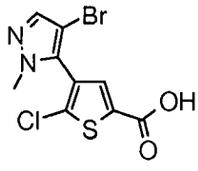
The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [(2S)-2-amino-2-phenylethyl]carbamate (57 mg, 0.24 mmol) [prepared according to the procedure of Preparation 1] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 396 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.42 (br. s., 1 H) 3.57 (d, *J*=11.12 Hz, 1H) 3.80 (s, 3 H) 5.44 (dd, *J*=10.36, 4.29 Hz, 1 H) 7.37 (d, *J*=2.53 Hz, 1 H) 7.40 - 7.47 (m, 2 H) 7.48 - 7.55 (m, 2 H) 7.60 (s, 1 H) 7.95 (br. s., 1 H).

Example 208



Preparation *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

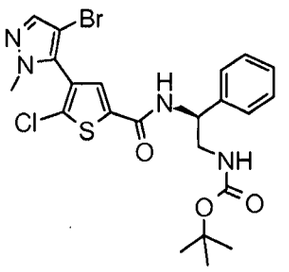
a) 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (300 mg, 1.169 mmol)[prepared according to the procedure of Example 193] in THF (10 ml) was added *N*-bromosuccinimide (212 mg, 1.19 mmol). The mixture was sealed and heated at 70 °C. After 2h, a solution of 6N NaOH (2.0 ml, 6.0 M, 11.84 mmol) was added in one portion. The resulting mixture

stirred for an additional 2h and was partitioned between DCM-H_2O. The pH of the aqueous phase was adjusted to ~3 and extracted several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated affording the title compound as a colorless oil (105 mg, 28%): LC-MS (ES) m/z= 322 $(M+H)^+$.

b) 1,1-dimethylethyl [(2*S*)-2-({[4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate



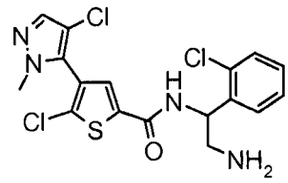
To a solution of 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxylic acid (80 mg, 0.25 mmol), 1,1-dimethylethyl [(2S)-2-amino-2-phenylethyl]carbamate (59 mg, 0.25 mmol) [prepared according to the procedure of Preparation 1], diisopropylethyl amine (128 uL, 0.75 mmol) in DCM (5 mL) was added PyBrop (168 mg, 0.36 mmol) in one portion. After 3h, the reaction contents were partitioned between H_2O/DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, gradient 0- 50% ethyl acetate / hexane) affording the title compound (110 mg, 0.18 mmol, 73%) as a white solid: LCMS (ES) m/z = 540 $(M+H)^+$.

c). *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (81 mg, 0.15 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.38 mL, 1.5 mmol) After 15h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as a white solid (18.3 mg, 0.04 mmol, 26%): LC-MS (ES) m/z 440 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.40 (d, *J*=13.89 Hz, 1H) 3.60 (br. s., 1

H) 3.80 (br. s., 3 H) 5.38 - 5.50 (m, 1 H) 7.37 (d, *J*=7.33 Hz, 1 H) 7.43 (t, *J*=7.45 Hz, 2 H) 7.52 (d, *J*=7.58 Hz, 2 H) 7.61 (s, 1 H) 8.02 (br. s., 1 H)

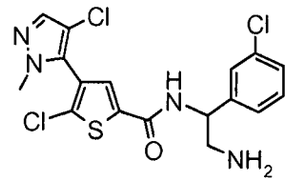
Example 209



Preparation *N*-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [2-amino-2-(3-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 430 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.45 (d, *J*=5.56 Hz, 2 H) 3.72 - 3.81 (m, 3 H) 5.86 (dd, *J*=9.22, 4.42 Hz, 1H) 7.41 (d, *J*=2.02 Hz, 2 H) 7.48 - 7.55 (m, 1 H) 7.58 (br. s., 2 H) 7.83 (s, 1 H)

Example 210

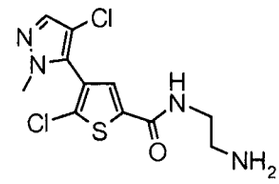


Preparation *N*-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [2-amino-2-(3-chlorophenyl)ethyl]carbamate (67 mg, 0.25 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 430 $(M+H)^+$, ^{1}HNMR (400 MHz, MeOD) δ ppm 3.44 (d, *J*=3.54 Hz, 1 H) 3.55 (d, *J*=10.61 Hz, 1 H) 3.80 (s, 3 H) 5.42

(dd, *J*=10.36, 4.29 Hz, 1 H) 7.35 - 7.49 (m, 3 H) 7.55 (s, 1 H) 7.59 (s, 1 H) 7.95 (d, *J*=14.40 Hz, 1 H)

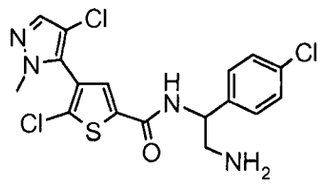
Example 211



Preparation *N*-(2-aminoethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl (2-aminoethyl)carbamate (58 mg, 0.36 mmol) for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 320 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.17 (d, *J*=5.81 Hz, 2 H) 3.66 (br. s., 2 H) 3.78 (s, 3 H) 7.60 (s, 1 H) 7.66 (s, 1H)

Example 212

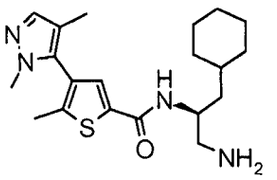


Preparation *N*-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 206, except substituting 1,1-dimethylethyl [2-amino-2-(4-chlorophenyl)ethyl]carbamate (65 mg, 0.24 mmol) [prepared according to the procedure of Preparation 16] for 1,1-dimethylethyl [2-amino-2-(4-fluorophenyl)ethyl]carbamate: LC-MS (ES) m/z 431 $(M+H)^+$, ^{1}HNMR (400 MHz, MeOD) δ ppm 3.43 (d, *J*=4.55 Hz, 1 H) 3.53 (d, *J*=10.11 Hz, 1 H) 3.79 (s, 3 H) 5.43

(dd, *J*=10.36, 4.55 Hz, 1H) 7.43 - 7.47 (m, 2 H) 7.48 - 7.53 (m, 2 H) 7.60 (s, 1 H) 7.94 (s,1 H)

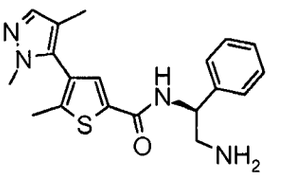
Example 213



Preparation *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

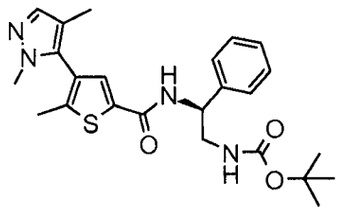
The title compound was prepared as an off-white solid according to the procedure of Example 99, except substituting 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione (73 mg, 0.25 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 0.91- 0.99 (m, 1H), 1.01-1.10 (m., 1 H) 1.39-1.47 (m., 3 H) 1.37-1.48 (m, 2 H) 1.65 - 1.77 (m, 5 H) 1.89 (br. s., 1 H) 2.10 (s, 3 H) 2.45 (s, 3 H) 3.07 - 3.16 (m, 2 H) 3.91 - 3.98 (m, 3 H) 4.42 (br. s., 1 H) 7.91 (br. s., 1 H) 8.24 (s, 1 H)

Example 214



Preparation *N*-[(1*S*)-2-amino-1-phenylethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

a) 1,1-dimethylethyl [(2*S*)-2-({[4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate

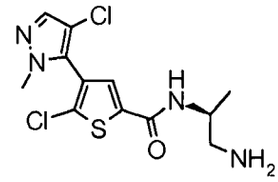


To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (110 mg, 0.4 mmol) [prepared in Experiment 99], 2-[(2S)-2-amino-4-methylpentyl]-1H-isoindole-1,3(2H)-dione (99 mg, 0.4mmol) [prepared according to the procedure of Preparation 1] and diisopropylethylamine (0.2 ml, 1.2 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (280 mg, 0.6 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound (113 mg, 0.22 mmol, 56 % yield) as a colorless oil: LC-MS (ES) m/e 506 (M+H)+.

d). *N*-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thienyl]carbonyl}amino)-2-phenylethyl]carbamate (99 mg, 0.22 mmol) in DCM (2 mL) was added 4N HCl solution in dioxane (0.5 mL, 2 mmol). After 15 h, the solution was extracted with water three times. The aqueous fractions were combined and concentrated to afford the di-HCl salt of the title compound as an off-white solid (40 mg, 0.11 mmol, 52%): LC-MS (ES) m/z 355 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.99 - 2.14 (m, 3 H) 2.43 (s, 3 H) 3.39 (d, *J*=9.85 Hz, 1 H)) 3.60 (d, *J*=9.85 Hz, 1 H) 3.92 (br. s., 3 H) 5.44 (d, *J*=8.84 Hz, 1 H) 7.36 (d, *J*=2.53 Hz, 1 H) 7.43 (t, *J*=5.94 Hz, 2 H) 7.49 - 7.57 (m, 2 H) 8.03 (br. s., 1 H) 8.14 (br. s., 1H).

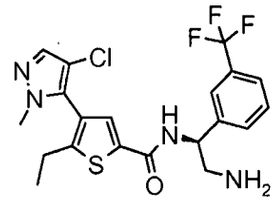
Example 215



Preparation *N*-[(1*S*)-2-amino-1-methylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 106, except substituting 2-[(2S)-2-aminopropyl]-1H-isoindole-1,3(2H)-dione (74 mg, 0.36 mmol) for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 333 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.37 (d, *J*=6.82 Hz, 3 H) 3.11 - 3.14 (m, 2 H) 3.79 (s, 3 H) 4.38 – 4.40 (m, 1 H) 7.60 (br. s., 1 H) 7.83 (d, *J*=2.27 Hz, 1 H).

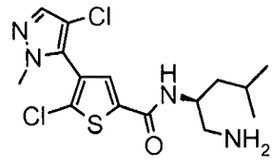
Example 216



Preparation *N*-{(1*S*)-2-amino-1-[3-(trifluoromethyl)phenyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 100, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (348 mg, 1.0 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 471 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.24 (t, *J*=7.33 Hz, 3 H) 2.54 (d, *J*=8.84 Hz, 2 H) 2.74 (q, *J*=7.24 Hz, 2 H) 3.05 - 3.16 (m, 1 H) 3.26 (d, *J*=4.80 Hz, 1 H) 3.66 - 3.79 (m, 3 H) 4.54 (br. s., 1 H) 7.47 - 7.56 (m, 2 H) 7.57 - 7.76 (m, 4 H).

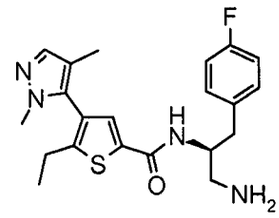
Example 217



Preparation *N*-[(1*S*)-1-(aminomethyl)-3-methylbutyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

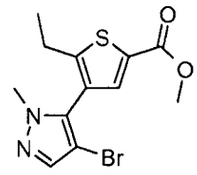
The title compound was prepared as an off-white solid according to the procedure of Example 106, except substituting 2-[(2S)-2-amino-4-methylpentyl]-1H-isoindole-1,3(2H)-dione (99 mg, 0.4 mmol) for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 376 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 0.99 (t, *J*=6.44 Hz, 6 H) 1.42 (s, 1 H) 1.63 - 1.80 (m, 2 H) 3.04 (br. s., 1 H) 3.14 (d, *J*=3.54 Hz, 1 H) 3.80 (s, 3 H) 4.42 (br. s., 1 H) 7.59 (s, 1 H) 7.84 (d, *J*=6.06 Hz, 1 H).

Experiment 218



Preparation *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

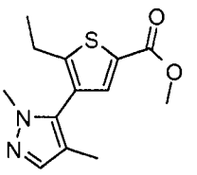
a) methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



To a solution of methyl 5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (600 mg, 2.40 mmol) [prepared according to Example 98] in Tetrahydrofuran (THF) (10 ml) was added N-bromosuccinimide (512 mg, 2.88 mmol). The mixture stirred in a sealed tube at 70 °C for 2h. The reaction mixture was then concentrated and purified with silica gel using a 0-5% gradient (ethyl

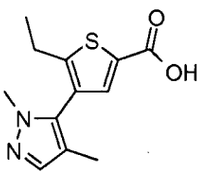
acetate / hexane) to afford the title compound as an off-white solid: LC-MS (ES) m/z 330 $(M+H)^+$.

b) methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate



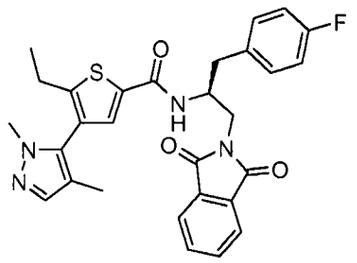
A solution of methyl 4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (635 mg, 1.93 mmol), potassium carbonate (1.33 g, 9.64 mmol), $PdCl_2$(dppf) (141 mg, 0.19 mmol) and trimethylboroxine (0.54 ml, 3.86 mmol) in N,N-dimethylformamide (3 ml) was stirred at 110 °C in a sealed tube for 2h. This reaction mixture was concentrated and partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (10-50% EtOAc in hexanes) affording the title compound (488 mg, 96%) as a yellow oil: LCMS (ES) m/e 265 (M+H)+.

c) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid



A solution of methyl 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylate (488 mg, 1.85 mmol) in 6N sodium hydroxide (3.08 ml, 18.5 mmol) and Tetrahydrofuran (10 ml) was stirred at 70 °C in a sealed tube for 1h. The resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the title compound as a yellow foam (448 mg, 1.79 mmol, 96 % yield) as a yellow oil: LCMS (ES) m/e 251(M+H)+.

d) 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-ethyl-2-thiophenecarboxamide

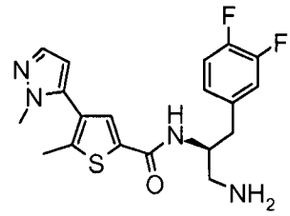


To a solution of 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxylic acid (250 mg, 1.0 mmol), 2-{(2S)-2-amino-3-[4-(fluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (313 mg, 1.05 mmol)[prepared according to the procedure of Preparation 6] and diisopropylethylamine (0.52 ml, 3 mmol) in DCM at 25 °C was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (746 mg, 1.6 mmol) in one portion. The solution stirred at 25 °C for 12h and was then partitioned between H_2O-DCM. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (silica, 30-70% EtOAc in hexanes) yielding the title compound as a yellow solid (490 mg, 0.92 mmol, 92 % yield) as a yellow foam: LCMS (ES) m/e 531 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide

To a solution of 4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(4-fluorophenyl)methyl]ethyl}-5-ethyl-2-thiophenecarboxamide (400 mg, 0.75 mmol) in methanol (8 ml) at 25 °C was added hydrazine (0.12 ml, 3.77 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was transferred to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as a yellow solid: LC-MS (ES) m/z 401 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 1.28 (t, *J*=7.58 Hz, 3 H) 2.07 (s, 3 H) 2.75 (m, 2 H) 3.02 (d, *J*=6.32 Hz, 2 H) 3.22 (br. s., 2 H) 3.92 (d, *J*=2.27 Hz, 3 H) 4.53 (br. s., 1 H) 7.02 (t, *J*=8.59 Hz, 2 H) 7.34 (m, 2H), 7.80 (s, 1 H) 8.13 - 8.25 (m, 1 H).

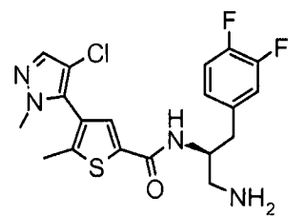
Example 219



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 103, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 391 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.44 (s, 3 H) 2.91 - 3.02 (m, 2 H) 3.16 (d, *J*=10.11 Hz, 1 H) 3.24 (dd, *J*=13.14, 3.54 Hz, 1H) 3.82 (s, 3 H) 4.50 (d, *J*=3.54 Hz, 1 H) 6.44 (d, *J*=2.02 Hz, 1H) 7.05 - 7.13 (m, 1 H)7.15-7.25 (m, 2H), 7.67-7.70 (m, 2 H) .

Example 220



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 102, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 425 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.40 (s, 3 H) 2.95 - 3.03 (m, 2 H) 3.23 - 3.26 (m, 2 H) 3.76 (br, s, 3H) 4.96 - 4.52 (m, 1H), 7.07 - 7.15 (m, 2H) 7.22 -7.28 (m, 1H) 7.55 - 7.77 (m, 2H).

NOV
1967

PATENTE DE INVENCIÓN

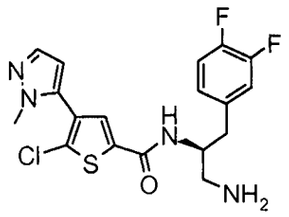
Organizacion y
Digitalizacion CSA Ltda

09-82387

3/5

82387/09

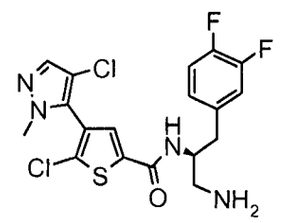
Example 221 T3



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a yellow solid according to the procedure of Example 104, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 411 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 3.02 (d, *J*=7.33 Hz, 2 H) 3.24 (d, *J*=6.82 Hz, 2 H) 4.01 (d, *J*=7.58 Hz, 3 H) 4.52 (d, *J*=7.07 Hz, 1 H) 6.78 (d, *J*=11.87 Hz, 1 H) 7.08 - 7.21 (m, 1 H) 7.26 - 7.28 (m, 1 H) 7.94 - 8.08 (m, 2 H).

Example 222

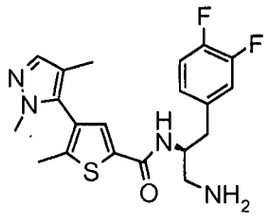


Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 106, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [Prepared according to the procedure of Preparation 6] for 2-[(2S)-2-amino-3-cyclohexylpropyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 446 $(M+H)^+$, ^1H

NMR (400 MHz, MeOD) δ ppm 2.95 - 3.05 (m, 2 H) 3.22 - 3.23 (m, 2 H) 3.79 (s, 3 H) 4.52 (br. s., 1 H) 7.08 - 7.21 (m, 2 H) 7.27 - 7.26 (m, 2 H) 7.60 (s, 1 H) 7.83 (br. s., 1 H) .

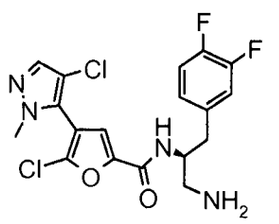
Example 223



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide

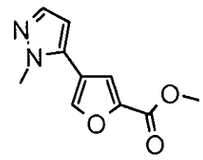
The title compound was prepared as a yellow solid according to the procedure of Example 99, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (332 mg, 1.05 mmol) [prepared according to Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 405 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.09 (s, 15 H) 2.42 (s, 3 H) 3.04 (d, *J*=7.07 Hz, 2 H) 3.27 (d, *J*=4.80 Hz, 2 H) 3.88 - 4.01 (m, 3H) 4.54 (br. s., 1 H) 7.08 - 7.21 (m, 2 H) 7.29 (d, *J*=7.58 Hz, 1 H) 7.92 (br. s., 1H) 8.15 - 8.26 (m, 1 H).

Example 224



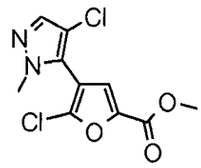
Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



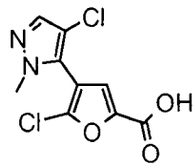
A solution of methyl 4-bromo-2-furancarboxylate (470 mg, 2.29 mmol), potassium carbonate (1584 mg, 11.46 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (525 mg, 2.52 mmol)[prepared according to Preparation 7] and bis-(tri-t-butylphosphine)Palladium (0) (58.6 mg, 0.12 mmol) in 1,4-dioxane (9.55 ml) and water (1.9 ml) was stirred at 80 °C. After 1hr, the solution was partitioned between H_2O-DCM and the aqueous phase was washed several times with DCM. The combined organic fractions were dried over Na_2SO_4, concentrated and purified via column chromatography (30% EtOAc in hexanes) affording the title compound (124 mg, 0.60 mmol, 26 % yield) as a white powder: LCMS (ES) m/e 206 $(M+H)^+$.

b) methyl 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate



A solution of methyl 4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (412 mg, 2.0 mmol) and N-chlorosuccinimide (267 mg, 2.0 mmol) in DMF (10 mL) was heated at 75 °C for 30 minutes. Another batch of N-chlorosuccinimide (267 mg, 2.0 mmol) was added. After 1 hr, the mixture was concentrated and purified using silica gel and eluting with 0-55% ethyl acetate / hexane to afford the title compound as a white solid (225 mg, 0.82 mmol, 71% yield) : LCMS (ES) m/e 276 $(M+H)^+$.

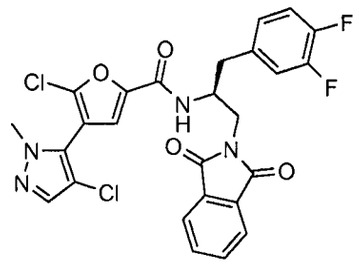
c) 5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylic acid



A solution of methyl 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (224 mg, 0.82 mmol) in 6N sodium hydroxide (1.36 ml, 8.2 mmol) and tetrahydrofuran (5 ml) was stirred at 70 °C in a sealed tube for 1h. The

resulting solution was cooled and then partitioned between H_2O-DCM. The aqueous phase was adjusted to pH ~4 and then washed several times with DCM. The combined organic fractions were dried over Na_2SO_4 and concentrated affording the title compound (201 mg, 0.77 mmol, 94 % yield) as a yellow oil: LCMS (ES) m/e 262 $(M+H)^+$.

d) 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide



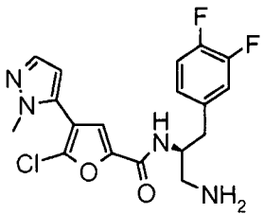
To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (200 mg, 0.77 mmol)[prepared according to the procedure of Preparation 6], 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (254 mg, 0.80 mmol) and N,N-diisopropylethylamine (0.40 ml, 2.30 mmol) in DCM (10 ml) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (536 mg, 1.15 mmol). After stirring at ambient temperature for 20 hrs, the mixture was concentrated and purified with silica gel column eluting with gradient (0-50% ethyl acetate/hexanes) to afford the title compounds as an off-white foamy solid (304 mg, 0.54 mmol, 71% yield): LCMS (ES) m/e 560(M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

To a solution of 5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide (304 mg, 0.54 mmol) in methanol (5 ml) at 25 °C was added hydrazine (0.08 ml, 2.7 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as a yellow solid: LC-MS (ES) m/z 430$(M+H)^+$, ^1H NMR (400 MHz,

MeOD) δ ppm 2.91 - 3.05 (m, 2 H) 3.17 - 3.28 (m, 2 H) 3.81 (s, 3 H) 4.57 (d, *J*=9.60 Hz, 1 H) 7.12 (br. s., 1 H) 7.18-7.28 (m., 2 H) 7.36-7.39 (m, 1 H) 7.58 (s, 1 H).

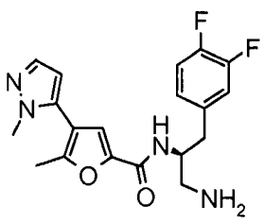
Example 225



Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

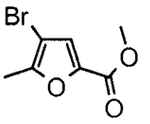
The title compound was prepared as an off-white solid according to the procedure of Example 127, except substituting 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (147 mg, 0.46 mmol) [prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.90 - 3.06 (m, 2 H) 3.18-3.24 (m, 2 H) 3.98 (d, *J*=17.68 Hz, 3 H) 4.52 - 4.64 (m, 1 H) 6.67 (d, *J*=1.77 Hz, 1 H) 7.19 (dd, *J*=10.11, 8.59 Hz, 2 H) 7.26 (td, *J*=9.73, 2.27 Hz, 1 H) 7.51 (d, *J*=19.96 Hz, 1 H) 7.93 (br. s., 1 H).

Example 226



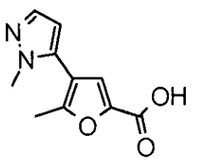
Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

a) methyl 4-bromo-5-methyl-2-furancarboxylate



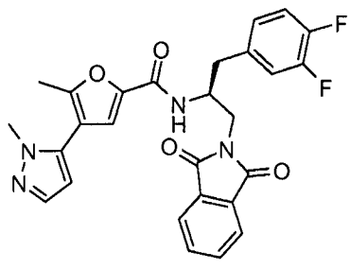
Methyl 4,5-dibromo-2-furancarboxylate (3.7 g, 13.03 mmol) [prepared according to Example 127] and trans-dichlorobis(triphenylphosphine)Palladium (II) (0.46 g, 0.65 mmol) were combined in THF (50ml) to give a yellow suspension. A THF solution of methylzinc chloride (11.40 ml, 22.81 mmol) was added dropwise at room temperature. After stirring at ambient temperature for 20h, the solution was concentrated and purified using silica gel and eluting with 0-30% ethyl acetate / hexane to generate the title compound as a white solid (1.45 g, 6.61 mmol, 51% yield): LC-MS (ES) m/z 220 $(M+H)^+$.

b) 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylic acid



To a solution of methyl 4-bromo-5-methyl-2-furancarboxylate (500 mg, 2.28 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (950 mg, 4.57 mmol)[prepared according to Preparation 7] and potassium carbonate (315 mg, 2.28 mmol) in 1,4-dioxane (8 mL) and water (2.0 mL) was added bis(tri-t-butylphosphine)Palladium (0) (117 mg, 0.23 mmol). The mixture was heated to 80 °C and after 15h the reaction mixture was concentrated. The residue was partitioned between DCM and water. The organic layer was concentrated and dissolved in tetrahydrofuran (THF) (8.0 mL). The solution was treated with 6N aqueous solution of sodium hydroxide (3.80 mL, 22.83 mmol) and heated to 75 °C. After 15h, the reaction mixture was concentrated and partitioned between DCM and water. The aqueous layer was acidified to pH ~ 3 with 2N HCl aqueous solution and extracted several times with DCM. The organic fractions were combined and concentrated to afford the title compound as a yellow solid (401 mg, 1.95 mmol, 85% yield): LC-MS (ES) m/z 207 $(M+H)^+$.

c) *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

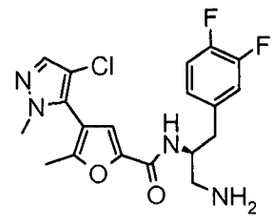


To a solution of 5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylic acid (200 mg, 0.97 mmol), 2-[(2S)-2-amino-3-(2,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (322 mg, 1.02 mmol)[prepared according to the procedure of Preparation 6] and N,N-diisopropylethylamine (0.51 ml, 2.91 mmol) in DCM (10 ml) was added bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (678 mg, 1.46 mmol). After stirring at ambient temperature for 20h, the mixture was concentrated and purified using silica gel and eluting with a 0-50% ethyl acetate/hexane gradient to afford the title compound as an off-white foamy solid (181 mg, 0.36 mmol, 37% yield): LCMS (ES) m/e 505 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

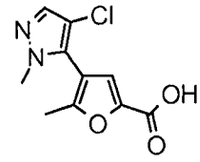
To a solution of *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide
(176 mg, 0.35 mmol) in methanol (5 ml) at 25 °C was added hydrazine (0.22 ml, 0.7 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as an off-white solid:
LC-MS (ES) m/z 430$(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.91 - 3.05 (m, 2 H) 3.17 - 3.28 (m, 2 H) 3.81 (s, 3 H) 4.57 (d, *J*=9.60 Hz, 1 H) 7.12 (br. s., 1 H) 7.18-7.28 (m., 2 H) 7.36-7.39 (m, 1 H) 7.58 (s, 1 H)

Example 227



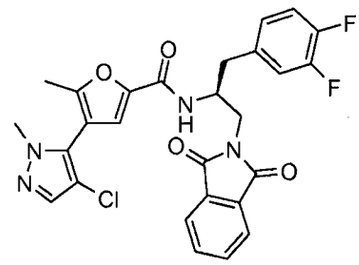
Preparation *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid



To a solution of 5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid (150 mg, 0.73 mmol)[prepared in Example 126] in THF (10 ml) was added N-chlorosuccinimide (97 mg, 0.73 mmol). After stirring at 70 °C for 20h in a sealed tube, the mixture was partitioned between H_2O-DCM and the pH of the aqueous phase was adjusted to ~4. The aqueous phase was washed several times with DCM and the combined organic fractions were dried over Na_2SO_4 and concentrated affording the title compound as an off-white foamy solid (152 mg, 0.63 mmol, 87% yield): LC-MS (ES) m/z 241$(M+H)^+$.

b) 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-furancarboxamide



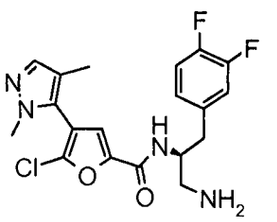
To a solution of 4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylic acid (150 mg, 0.62 mmol) , 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (207 mg, 0.65 mmol)[prepared according to the procedure of Preparation 6] and N,N-diisopropylethyl amine (0.33 ml, 1.87 mmol) in DCM (10 ml) was added bromo-tris-pyrrolidino-phosphonium

hexafluorophosphate (436 mg, 0.94 mmol). After stirring at ambient temperature for 20h, the mixture was concentrated and purified using silica gel and eluting with a gradient of 0-50% ethyl acetate/hexane to afford the title compound as an off-white foam (200 mg, 0.35 mmol, 57% yield): LC-MS (ES) m/z 539 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

To a solution of 4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-furancarboxamide (210 mg, 0.39 mmol) in methanol (5 ml) at 25 °C was added hydrazine (0.02 ml, 0.78 mmol) dropwise. After 12h, the solution was concentrated, dry loaded onto silica and purified by column chromatography (5% MeOH in DCM (1% NH_4OH)). The free base was converted to the HCl salt by addition of excess 4M HCl in dioxane (1 ml) to the residue in MeOH (2 ml) affording the HCl salt of the title compound as an off-white solid: LC-MS (ES) m/z 409$(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.38 (s, 3 H) 2.98 (d, *J*=9.35 Hz, 1 H) 3.01 (d, *J*=5.56 Hz, 1 H) 3.23 (dd, *J*=13.01, 8.97 Hz, 2 H) 3.73 - 3.83 (m, 3 H) 4.56 (d, *J*=9.35 Hz, 1H) 7.17 (s, 1 H) 7.18 - 7.32 (m, 3 H) 7.57 (s, 1 H).

Example 228

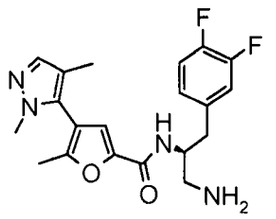


Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 118, except substituting 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (253 mg, 0.8 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 409

$(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.05 - 2.15 (m, 3H) 2.91 - 3.07 (m, 2 H) 3.16 - 3.26 m., 2 H) 3.91 (br. s., 3 H) 4.57 - 4.59 (m., 1 H) 7.09 - 7.31 (m, 3 H) 7.51 (br. s., 1 H) 8.07 (br. s., 1 H)

Example 229

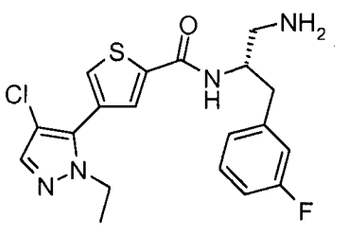


Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

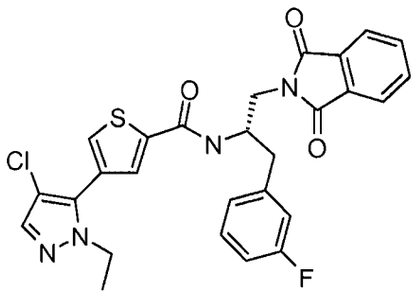
The title compound was prepared as a yellow solid according to the procedure of Example 119, except substituting 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (302 mg, 0.95 mmol)[prepared according to the procedure of Preparation 6] for 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 389 $(M+H)^+$, ^1H NMR (400 MHz, MeOD) δ ppm 2.04 - 2.15 (m, 3 H) 2.35 - 2.47 (m, 3 H) 2.99 - 3.02 (m,, 2 H) 3.18 - 3.24 (m, 2 H) 3.86 - 3.96 (m, 3 H) 4.56 - 4.62 (m, 1H) 7.16 - 7.26 (m, 4 H) 8.07 (s, 1 H).

Example 230

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

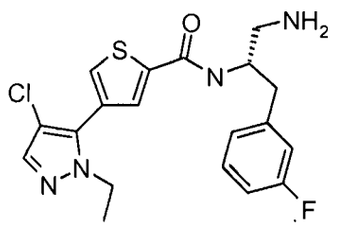


a) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (220 mg, 0.857 mmol) [from Example 92] in DCM (5 mL) at 25 °C was added PyBrOP (440 mg, 0.857 mmol) in one portion, followed by addition of DIPEA (1.5 mL, 8.59 mmol). After 10 min, diamine 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (256 mg, 0.857 mmol) was added to above solution. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (0.39 g, 81%) as a white solid: LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



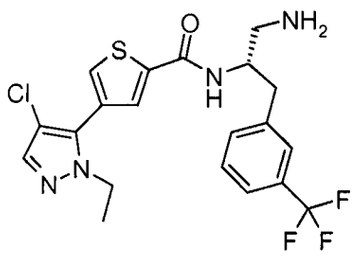
At RT, NH_2NH_2 (0.11 mL, 3.54 mmol) was added to 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (380 mg, 0.708 mmol) in MeOH (4 mL). After 10h, the solvent was removed under vaccum to give a residue, which was dissolved in DCM (15 mL), and washed with H_2O (10 mL x 3).

To the above DCM solution was added aqueous HCl (12 N, 2.95 mL, 35.4 mmol). After 1h, the aqueous phase was separated, and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (160 mg, 47%) as a white solid: LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 9.18-8.8(m, 1H), 8.28-8.08 (m, 4H), 8.04 (s, 1H), 7.27-7.43 (m, 1),

7.08-7.24 (m, 2H), 6.91-7.08 (m, 1H), 4.4-4.34 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 3.15-2.80 (m, 4H), and 1.29 (t, J = 7.3 Hz, 3H).

Example 231

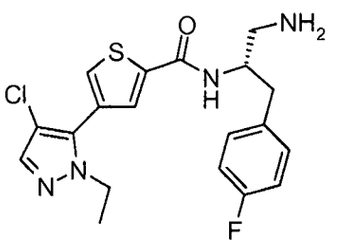
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 230, except substituting 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (339 mg, 0.97 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z = 457 $(M+H)^+$, ^{1}H NMR (d_4-MeOD, 400 MHz) δ ppm 7.92 (br s, 1H), 7.89-7.80 (m, 1H), 7.63-7.59 (m, 3H), 7.56-7.48 (m, 2H), 4.61-4.53 (m, 1H), 4.21-4.15 (m, 2H), 3.46-3.21 (m, 2H), 3.18-3.02 (m, 2H), and 1.35 (t, J = 7.3 Hz, 3H).

Example 232

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

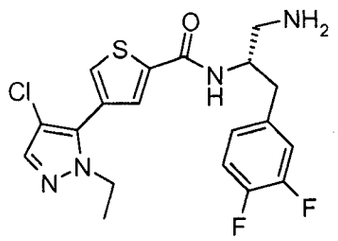


The title compound was prepared as an off-white solid according to the procedure of Example 230, except substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (584 mg, 1.95 mmol) for 2-[(2S)-2-

amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.93 (d, J = 1.3 Hz, 1H), 7.85 (d, J = 1.3 Hz, 1H), 7.59 (s, 1H), 7.34-7.31 (m, 2H), 7.05-7.01 (m, 2H), 4.52 (m, 1H), 4.19 (q, J = 7.3 Hz, 2H), 3.26-3.12 (m, 2H), 3.05-2.94 (m, 2H), and 1.36 (t, J = 7.3 Hz, 3H).

Example 233

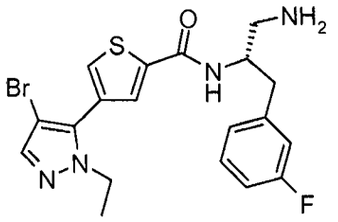
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



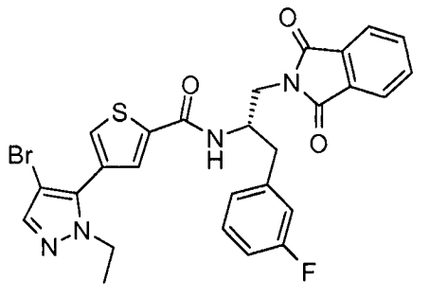
The title compound was prepared as an off-white solid according to the procedure of Example 230, except substituting 2-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (200m g, 0.63 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z = 425$(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 8.88 (d, J = 8.3 Hz, 1H), 8.16-8.06 (m, 4H), 7.71 (s, 1H), 7.39-7.30 (m, 2H), 7.12 (m, 1H), 4.35 (m, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.08-2.87 (m, 4H), and 1.29 (t, J = 7.1 Hz, 3H).

Example 234

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

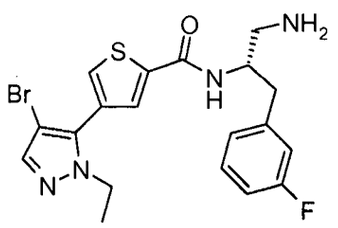


a) 4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 93, except substituting 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (149 mg, 0.50 mmol) for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z = 582 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

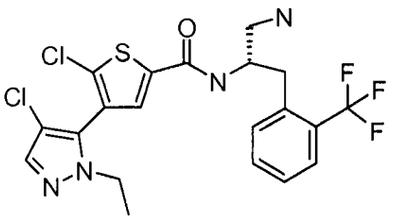


The title compound was prepared as an off-white solid according to the procedure of Example 230(b), except substituting *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (240 mg, 0.41 mmol) for 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide: LC-MS (ES) m/z = 452$(M+H)^+$,

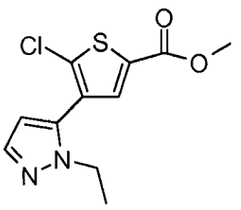
^{1}H NMR (d_6-DMSO, 400 MHz) δ ppm 9.24-8.85 (m, 1H), 8.26-8.13 (m, 4H), 8.03 (s, 1H), 7.03 (s, 1H), 7.34 -7.29 (m, 1H), 7.16-7.13 (m, 2H), 7.05-7.00 (m, 1H), 4.39 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 3.06-2.96 (m, 4H), and 1.28 (t, J = 7.3 Hz, 3H).

Example 235

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

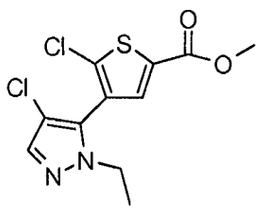


a) Methyl 5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



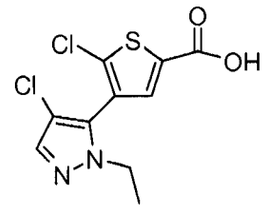
To a solution of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (300 mg, 1.17 mmol) in THF (2 mL) was added Na_2CO_3 (2M, 1.76 mL, 3.52 mmol), $Pd(dppf)Cl_2$ (86, 0.117 mmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (313 mg, 1.41 mmol). The reaction mixture was heated to 80 °C in a sealed tube under N_2. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-50%) to afford the title compound (0.272 g, 82%) as a light yellow syrup: LC-MS (ES) m/z = 271 $(M+H)^+$.

b) Methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



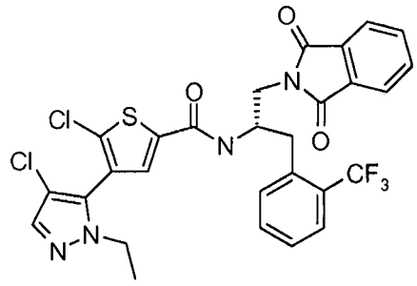
Methyl 5-chloro-4-[(1Z)-1-(1-ethyl-2-methylidenehydrazino)-1-propen-1-yl]-2-thiophenecarboxylate (260 mg, 0.96 mmol) and 1-chloro-2,5-pyrrolidinedione (154 mg, 1.15 mmol) in THF (4 mL) were heated at 70 °C under N_2 for 2 h, concentrated and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (0.281g, 83%) as a syrup: LC-MS (ES) m/z = 305 $(M+H)^+$.

c) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (260 mg, 0.85 mmol) in THF/H_2O (4 mL/1 mL) was added KOH (478 mg, 8.52 mmol). The reaction mixture was heated to 50° C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly without further purification.

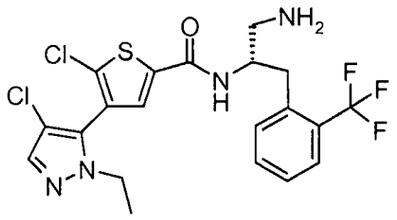
d) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (~0.85 mmol) in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (477 mg, 1.02 mmol) in one portion, followed by the addition of DIPEA (0.744 mL, 4.26 mmol). After stirring for 10 min, diamine 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (356 mg, 1.02 mmol) was added to the above solution.

After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (0.416 g, 79%) as a white solid: LC-MS (ES) m/z = 621 $(M+H)^+$.

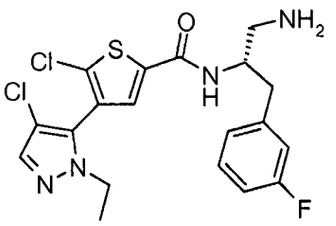
e) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



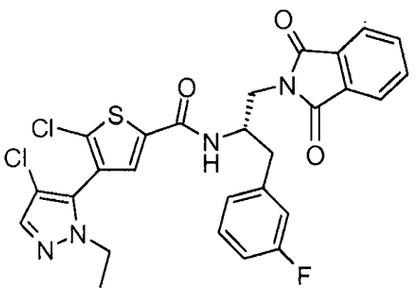
5-Chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (410 mg, 0.66 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (1.04mL, 33 mmol). The reaction was stirred over 5h at RT, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95 -5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water and neutralized by ammonium hydroxide. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound, which was dissolved in MeOH (2 mL), and treated with HCl (4 M in dioxane, 1.6 mL). After stirring overnight, the reaction solution was concentrated to give the title compound (160 mg, 42 %) as a di-HCl salt: LC-MS: m/z = 491 $(M+H)^+$,^{1}H NMR (d_6-DMSO, 400 MHz) δ ppm 9.34 (J = 8.8 Hz, 1H), 8.38-8.03 (m, 3H), 7.77 (s, 1H), 7.69-7.59 (m, 2H), 7.53 (dd, J = 7.3, 7.3 Hz, 1H), 7.42(dd, J = 7.6, 7.6 Hz, 1H), 4.48 (m, 1H), 4.13-4.00 (m, 2H), 3.17-2.90 (m, 4H), and 1.29 (m, 3H).

Example 236

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

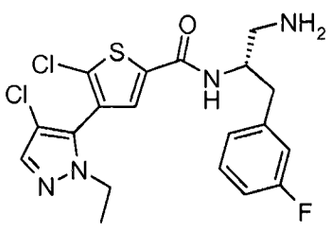


a) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a solution of 5-chloro-4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (180 mg, 0.618 mmol) [from Example 235(c)] in DCM (5 mL) at 25 °C was added PyBrOP in one portion, followed by addition of DIPEA (0.54 mL, 3.09 mmol). After stirring for 10 min, 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (203 mg, 0.68 mmol) was added to above solution in one portion. After stirring for 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (285 mg, 77%) as a white solid: LC-MS (ES) m/z = 571 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

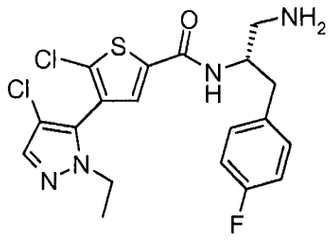


At RT, NH_2NH_2 (0.15 ml, 4.78 mmol) was added to 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (280 mg, 0.49 mmol) in MeOH

(5 mL). After 10h the solvent was removed under vaccum. The resulting residue was dissolved in DCM (15 mL), and washed with H_2O (10 mL x 3). To the DCM solution was added HCl (12 N, 1.0 mL). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the tilte compound (179 mg, 67.5%) as an off-white solid: LC-MS (ES) m/z = 441 $(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz) δ ppm 7.72-7.67 (m, 1H), 7.62 (s, 1H), 7.35-7.29 (m, 1H), 7.14-7.17 (m, 2H), 7.00-6.96 (m, 1H), 4.53 (m, 1H), 4.14-3.97 (m, 2H), 3.37-3.15 (m, 2H), 3.07-2.97 (m, 2H), and 1.33 (t, J = 7.1 Hz, 3H).

Example 237

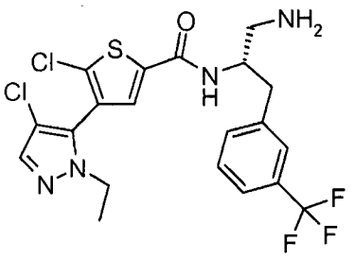
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound (190 mg, 70%) was prepared as an off-white solid according to the procedure of Example 236, except substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (231 mg, 0.77 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 441$(M+H)^+$, ^1H NMR (d_4-MeOD, 400 MHz, no calibration of chemical shift of MeOD solvent peak) δ ppm 6.09 (s, 1H), 6.08 (s, 1H), 5.78-5.75 (m, 2H), 5.53-5.48 (m, 2H), 2.96 (m, 1H), 2.51 (m, 2H), 1.71-1.67 (m, 1H), 1.62-1.54 (m, 1H), 1.49-1.38 (m, 2H), and -0.21 (t, J = 7.3 Hz, 3H).

Example 238

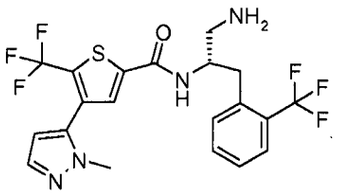
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



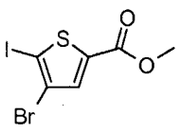
The title compound (228 mg, 58.2%) was prepared as an off-white solid according to the procedure of Example 236, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (156 mg, 0.45 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 491(M+H)$^+$, ^{1}H NMR (d_4-MeOD, 400 MHz) δ ppm 7.66-7.49 (m, 6H), 4.60-4.47 (m, 1H), 4.09-4.01 (m, 2H), 3.36-3.18 (m, 2H), 3.16-3.01 (m, 2H), and 1.33 (t, J = 7.1 Hz, 3H).

Example 239

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide

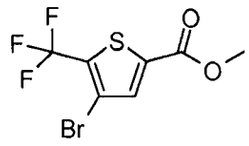


a) methyl 4-bromo-5-iodo-2-thiophenecarboxylate



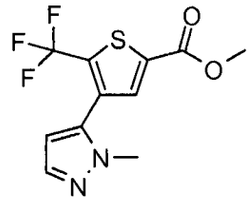
At -78 °C, nBuLi (2.05 mL, 5.13 mmol) was added to a solution of methyl 4,5-dibromo-2-thiophenecarboxylate (1.4 g, 4.67 mmol) in THF (10 mL). After the mixture was stirred for 30 min, I_2 (1.185 g, 4.67 mmol) was added in 3 mL THF. After the resulting solution was stirred at -78 °C for 1h, it was quenched with $Na_2S_2O_3$ at -78 °C, and warmed to RT. The reaction mixture was extracted with DCM, dried over Na_2SO_4, and concentrated. The crude product was purified on silica (EtOAc/Hex, 0-10%) to give the title compound (1.3 g, 56 %) as a yellow solid: LC-MS (ES) m/z 348(M+H)$^+$.

b) methyl 4-bromo-5-(trifluoromethyl)-2-thiophenecarboxylate



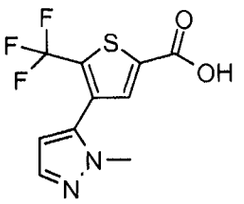
To a solution of methyl 4-bromo-5-iodo-2-thiophenecarboxylate (500 mg, 1.44 mmol), copper (I) iodide (137 mg, 0.72 mmol) and potassium fluoride (251 mg, 4.32 mmol) in DMF/HMPA (5 ml/5 mL) was added methyl difluoro(fluorosulfonyl)acetate (1.1g, 5.76 mmol). The mixture was heated at 70 °C under N_2 in a sealed tube. After 1h, the reaction was quenched with NH_4Cl (sat'd) (2 mL), extracted with ether (5 mL x 5) and washed with distilled water (5 mL x 5). The combined organic phase was dried over Mg_2SO_4 and purified on silica (EtOAc/Hex, 20-50%) to afford the title compound (0.82 g) containing a 60% inseparable impurity: LC-MS m/z (ES) 290 $(M+H)^+$.

c) methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylate



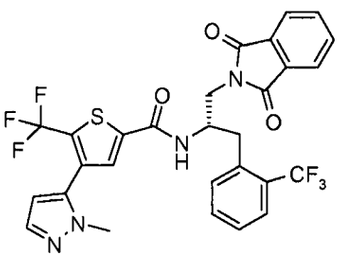
A mixture of methyl 4-bromo-5-(trifluoromethyl)-2-thiophenecarboxylate (0.8 g, 40% purity, 1.11 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (0.299 g, 1.434 mmol), tetrakis (0.128 g, 0.11 mmol) and K_2CO_3 (0.459 g, 3.32 mmol) in dioxane/H_2O (5 mL/1 mL) was heated to 70° C in a sealed tube. After 12h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 40-60%) to afford the title compound (0.25 g, 70%) as a light yellow solid: LC-MS (ES) m/z 291 $(M+H)^+$.

d) 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylic acid



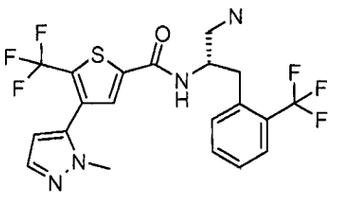
To a solution of methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylate (250 mg, 0.77 mmol), in THF/H_2O (3 mL/0.3 mL), was added KOH (217 mg, 3.88 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were concentrated under vacuum to give crude acid (235 mg, 80% pure) which was used directly in the next step without further purification: LC-MS (ES) 277 $(M+H)^+$.

e) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide



At room temperature, a mixture of 4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxylic acid (235 mg, 80% purity, 0.68 mmol), phosphoniumhexafluorophosphate (PyBrOP) (381 mg, 0.19 mmol), DIPEA (0.59 mL, 3.4 mmol) and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (261 mg, 0.75 mmol) in DCM (5 mL) was stirred for 2h. The reaction solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (386 mg, 86%) as a white solid: LC-MS (ES) 607 $(M+H)^+$.

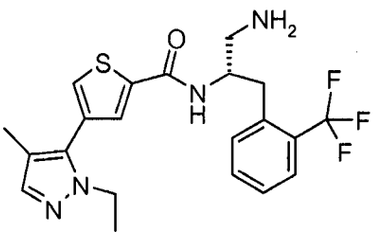
f) N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide



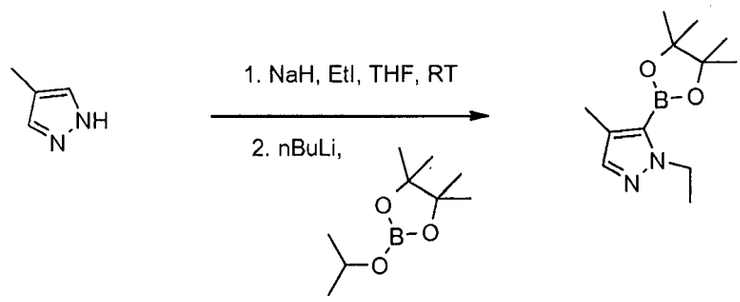
N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide (150 mg, 0.25 mmol) was dissolved in MeOH (5 mL) and was treated with NH_2NH_2 (0.76 mL, 24.2 mmol). The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95 -5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water, and ammonium hydroxide (0.32 mL, 30% wt%, 2.46 mmol) was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (2 mL), and treated with HCl (4 M in dioxane, 0.62 mL, 2.48 mmol). After stirring overnight, the reaction solution was concentrated to give the title compound (90 mg, 66%) as a white solid: LC-MS (ES) m/z 477 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 8.00 (d, J = 1.1 Hz, 1H), 7.77 (d, J = 1.8 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.59-7.52 (m, 2H), 7.44 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 4.67 (m, 1H), 3.87 (s, 3H), and 3.37-3.14 (m, 4H).

Example 240

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



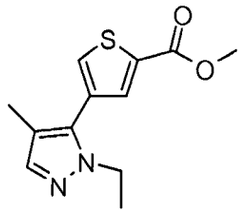
a) 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



To a suspension of NaH (4.3 g, 60%, 108 mmol) in THF (200 mL) at RT was added 4-methyl-1H-pyrazole (6.8 g, 83 mmol) dropwise. After 30 min, EtI (8.03 mL, 99 mmol) was added dropwise. After the reaction was complete (2h), the reaction solution was diluted with saturated aqueous NH_4Cl and extracted with ether. The ether fractions, were washed with water (3 x 100 mL), and dried over $MgSO_4$.

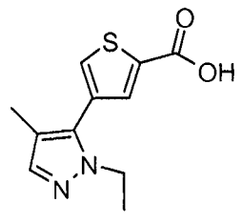
At 0°C, to the above ether solution of 4-methyl pyrazole was added n-BuLi (36.4 mL, 2.5 M in Hexane, 91 mmol) dropwise. The reaction solution was stirred for 1 hour at RT and then cooled to -78 °C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18.49 g, 99 mmol). After 15 min at -78°C, the reaction was allowed to warm to 0°C over 1hour. The reaction was diluted with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (16 g, 80% purity) as a syrup which was used without further purification: LC-MS (ES) m/z 155 $(M+H)^+$ for [RB(OH)2].

b) methyl 4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



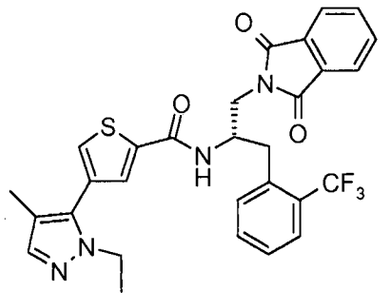
A mixture of methyl 4-bromo-2-thiophenecarboxylate (300 mg, 1.36 mmol), 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (449 mg, 1.9 mmol), $Pd(Ph_3P)_4$ (157mg, 0.136 mmol), and K_2CO_3 (536 mg, 4.07 mmol) was heated at 70 °C for 2h, concentrated and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (0.27 g, 79%) as a syrup: LC-MS m/z = 251 $(M+H)^+$.

c) 4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



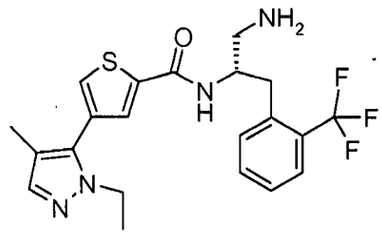
To a solution of methyl 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (270 mg, 1.08 mmol) in THF/H_2O (2 mL/0.4 mL) was added KOH (303 mg, 1.79 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid (240 mg), which was used directly in the next step without further purification: LC-MS m/z = 237 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a mixture of 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (240 mg, 1.02 mmol) and bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (Pybrop) (568 mg, 1.22 mmol) was added DIPEA (1.77 ml, 10.16 mmol). After 10 min, 2-{(2S,4Z)-2-amino-4-[(1E)-1-(trifluoromethyl)-1-propen-1-yl]-4,6-heptadien-1-yl}-1H-isoindole-1,3(2H)-dione (425 mg, 1.22 mmol) was added. After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (365 mg, 63%) as a white solid: LC-MS (ES) m/z 567 $(M+H)^+$.

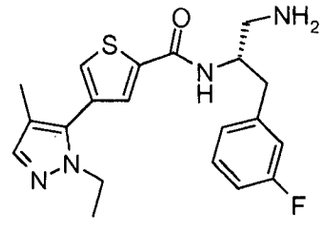
e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



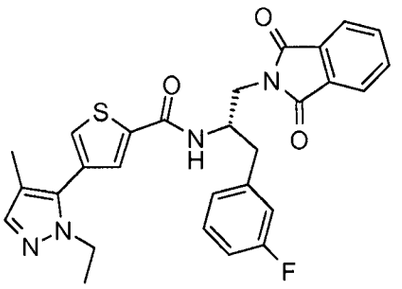
N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (365 mg, 0.64 mmol) was dissolved in MeOH (8 mL) and was treated with NH_2NH_2 (0.1 mL, 3.22 mmol). The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water, and ammonium hydroxide (4.18 mL, 30% wt%, 32.2 mmol) was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (2 mL) and treated with HCl (4 M in dioxane, 3.22 mL, 12.88 mml). After stirring overnight, the reaction solution was concentrated to give the title compound (190 mg, 56.7%) as a white solid: LC-MS (ES) m/z 437 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.96 (m, 1H), 8.17-8.04 (m, 4H), 7.87 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.62 (m, 1H), 7.53 (dd, J = 7.3, 7.3 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.38 (s, 1H), 4.50 (m, 1H), 4.09 (q, J = 7.3 Hz, 2H), 3.18-2.98 (m, 4H), 2.00 (s, 3H), and 1.27 (t, J = 7.3 Hz, 3H).

Example 241

(*N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

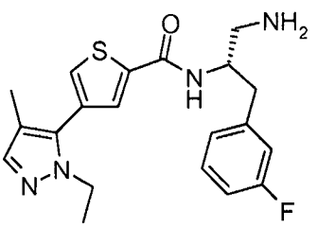


a) N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (125 mg, 0.53 mmol) [from Example 240(c)] in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate(PyBrOP) in one portion (350 mg, 0.75 mmol), followed by addition of DIPEA (0.7 ml, 4.0 mmol). After 10 min, 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (180 mg, 0.60 mmol) was added to above solution. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (258 mg, 94%) as a white solid: LC-MS (ES) m/z 517 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



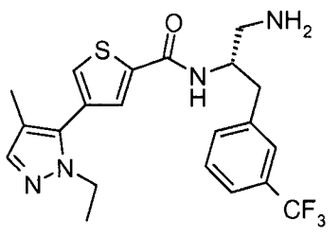
At RT, NH_2NH_2 (0.1 mL, 3.19 mmol) was added to N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (252 mg, 0.49 mmol) in MeOH (5 ml). After 10h, the solvent was removed under vacuum. The resulting residue was dissolved in DCM (10 mL) and washed with H_2O (10 mL x 3).

To the above DCM solution was added HCl (36%, 2 mL). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was

removed under high vacuum to give the title compound (170 mg, 72%) as an off-white solid: LC-MS(ES) m/z 387 $(M+H)^+$. NMR (d_6-DMSO, 400 MHz) δ ppm 8.87 (d, J = 8.9 Hz, 1H), 8.08 (br s, 2H), 8.01 (s, 1H), 7.08 (s, 1H), 7.37 (s, 1H), 7.35-7.29 (m, 1H), 7.16-7.10 (m, 2H), 7.05-7.00 (m, 1H), 4.38 (m, 1H), 4.07 (q, J = 7.3 Hz, 2H), 3.04-2.94 (m, 4H), 2.00 (s, 3H), and 1.26 (t, J = 7.3 Hz, 3H).

Example 242

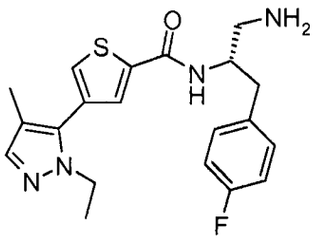
N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound (180 mg, 67%) was prepared as an off-white solid according to the procedure of Example 241, except substituting 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (220 mg, 0.63 mmol) for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z 437 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.96 (d, J = 8.84 Hz, 1H), 8.15 (m, 2H), 8.04 (d, J =1.3 Hz, 1H), 7.86 (d, J = 1.3 Hz, 1H), 7.69-7.49 (m, 4H), 7.36 (s, 1H), 4.39 (m, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.11-3.00 (m, 4H), 1.99 (s, 3H), and 1.25 (t, J = 7.1 Hz, 3H).

Example 243

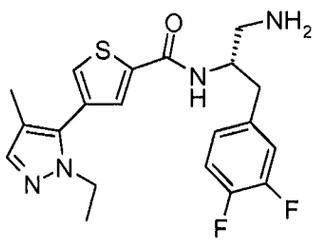
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



The title compound was prepared as an off-white solid according to the procedure of Example 241, except substituting 2-[(2*S*)-2-amino-3-(4-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (160 mg, 0.536 mmol) for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z 387 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.90 (d, J = 8.6 Hz, 1H), 8.13 (m, 2H), 8.03 (d, J =1.3 Hz, 1H), 7.87 (d, J = 1.3 Hz, 1H), 7.38-7.30 (m, 3H), 7.12-7.08 (m, 2H), 4.36 (m, 1H), 4.07 (q, J = 7.1 Hz, 2H), 3.07-2.97 (m, 2H), 2.96-2.88 (m, 2H), 2.00 (s, 3H), and 1.25 (t, J = 7.1 Hz, 3H).

Example 244

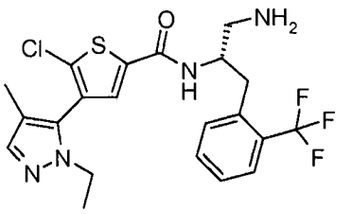
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



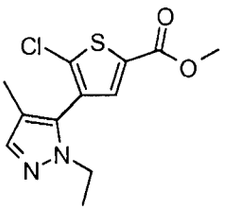
The title compound (210 mg, 72%) was prepared as an off-white solid according to the procedure of Example 241, except substituting 2-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (240 mg, 0.76 mmol) for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione: LC-MS (ES) m/z 405 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz) δ ppm 8.99 (d, J = 8.34 Hz, 1H), 8.16 (m, 2H), 8.09 (d, J =1.0 Hz, 1H), 7.87 (d, J = 1.0 Hz, 1H), 7.40-7.30 (m, 3H), 7.13 (br s, 1H), 4.36 (m, 1H), 4.08 (q, J = 7.3 Hz, 2H), 3.06-2.99 (m, 2H), 2.96-2.33 (m, 2H), 2.00 (s, 3H), and 1.26 (t, J = 7.3 Hz, 3H).

Example 245

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

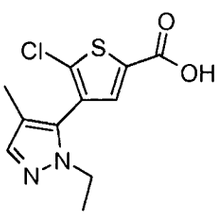


a) Methyl 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



A mixture of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (230 mg, 0.9 mmol), 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (425 mg, 1.8 mmol), $PdCl_2$(dppf) (65.9 mg, 0.09 mmol), and sodium carbonate (2N aq, 1.35 mL, 2.7 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. Afte 5h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 40-60%) to afford the title compound (241 mg, 92%) as a light yellow solid: LC-MS (ES) m/z = 285 $(M+H)^+$.

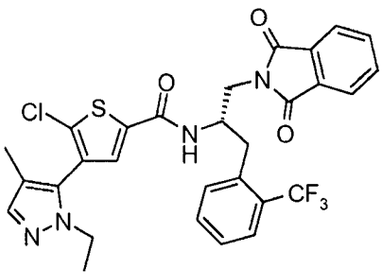
b) 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



To a solution of methyl 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (260 mg, 0.90 mmol) in THF/H_2O (2 mL/2 mL) was added KOH (201 mg, 3.6 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were

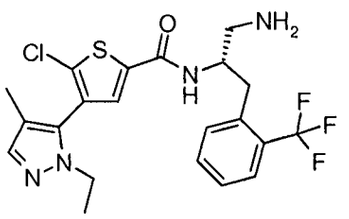
concentrated under vacuum to give crude 5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid, which was used directly without further purification: LC-MS (ES) m/z 271 $(M+H)^+$.

c) 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (542 mg, 1.16 mmol) in one portion, followed by addition of DIPEA (0.16 mL, 0.90 mmol). After 10 min, 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (312 mg, 0.90 mmol) was added in one portion. After 2h, the reaction solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (278 mg, 49 % for two steps) as a white solid: LC-MS (ES) m/z 601 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

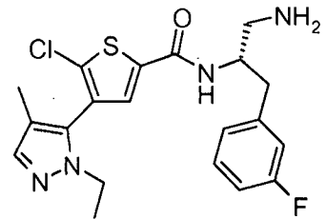


5-Chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (255 mg, 0.42 mmol) was dissolved in MeOH (2mL) and was treated with NH_2NH_2 (0.13 mL, 4.2 mmol). The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-

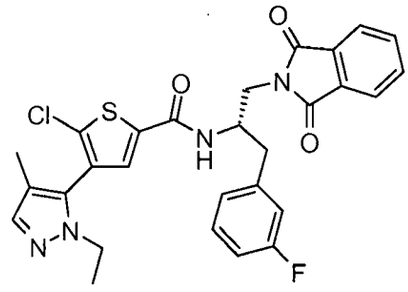
5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissolved in water and ammonium hydroxide was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (1 mL) and treated with HCl (4 M in dioxane, 2.1 mL). After stirring overnight, the mixture was concentrated to give 120 mg of the title compound (120 mg, 49%) as an off-white solid: LC-MS (ES) m/z 471 (M+H)+, ^{1}H NMR (d_4-MeOD, 400 MHz) δ ppm 7.91 (br s, 2h), 7.71 (m, 1H), 7.59 (m, 1H), 7.53 (m, 1H), 7.44 (m, 1H),·4.65 (m, 1H), 4.21(m, 2H), 3.37-3.14 (m, 4H), 2.07 (s, 3H), and 1.40 (m, 3H).

Example 246

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



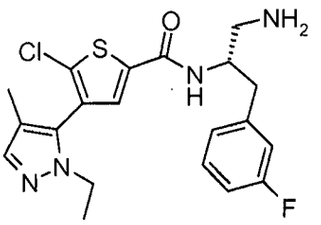
a) 5-chloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



To a solution of 5-chloro-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxylic acid (130 mg, 0.48 mmol) [from Example 245(b)] in DCM (5 mL) at 25 °C was added PyBrOP (250 mg, 0.54 mmol) in one portion, followed by addition of DIPEA (0.7 mL, 4.01 mmol). After 10 min, 2-[(2S)-2-amino-3-(3-

fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (150 mg, 0.50 mmol) was added to above solution. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (210 mg, 79%) as a white solid: LC-MS m/z (ES) 551 $(M+H)^+$.

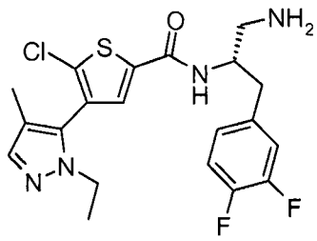
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



At RT, NH_2NH_2 (0.1 mL, 3.19 mmol) was added to 5-chloro-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (201 mg, 0.36 mmol) in MeOH (3 mL) . After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (10 mL) and washed with H_2O (10 mL x 3). To the DCM solution was added HCl (36%, 2 mL). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (101 mg, 53%) as an off-white solid: LC-MS (ES) m/z 421 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 9.02 (d, J = 8.3 Hz, 1H), 8.08 (s, 2H), 7.97 (s, 1H), 7.42 (s, 1H), 7.32 (m, 1H), 7.15-7.09 (m, 1H), 7.06-7.01 (m, 1H), 4.35 (m, 1H), 3.95 (m, 2H), 3.05-2.98 (m, 2H), 2.96-2.88 (m, 2H), and 1.92 (s, 3H), and 1.24 (t, J = 6.6 Hz, 3H).

Example 247

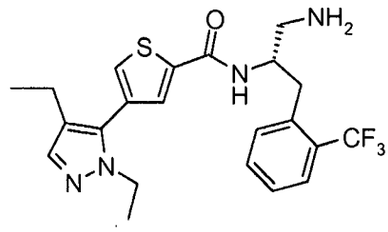
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



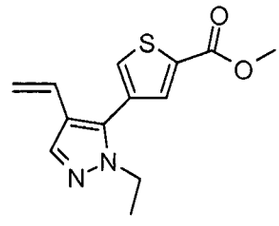
The title compound (95 mg, 50.2%) was prepared according to the procedure of Example 246, except substituting 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (152 mg, 0.48 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 439 $(M+H)^+$,^{1}H NMR (d_6-DMSO, 400 MHz) δ ppm 9.10 (d, J = 8.6 Hz, 1H), 8.13 (s, 2H), 8.03 (s, 1H), 7.42 (s, 1H), 7.39-7.30 (m, 2H), 7.15-7.10 (m, 1H), 4.33 (m, 1H), 3.95 (m, 2H), 3.05-2.99 (m, 2H), 2.96-2.88 (m, 2H), 1.92, and 1.24 (t, J = 6.3 Hz, 3H).

Example 248

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



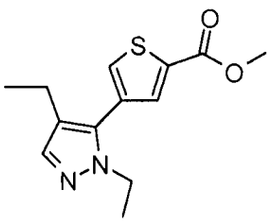
a) Methyl 4-(4-ethenyl-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



A mixture of methyl 4-(4-bromo-1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (200 mg, 0.64 mmol), $Pd(Ph_3P)_4$ (73.3 mg, 0.06 mmol), and tributyl(ethenyl)stannane (302 mg, 0.95 mmol) was heated at 90 °C for 1 h under N_2

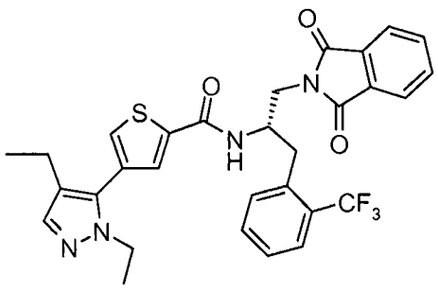
in a sealed tube. The mixture was purified on Silica (10%-20% EtOAc in Hex) to give the title compound (151 mg, 76%): LC-MS (ES) m/z 263 $(M+H)^+$.

b) Methyl 4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



Pd/C (12 mg, 10%) was added to a solution of ethyl 4-(4-ethenyl-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (150 mg, 0.57 mmol) in EtOH. The air in the system was removed by vacuum. The reaction mixture was stirred for 10h under a balloon of hydrogen gas. The reaction was diluted with MeOH (2 mL) and filtered through Celite. Concentration of the reaction solution gave the title compound (149 mg, 94%) as a yellow oil: LC-MS (ES) m/z 265 $(M+H)^+$.

c) 4-(1,4-diethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide

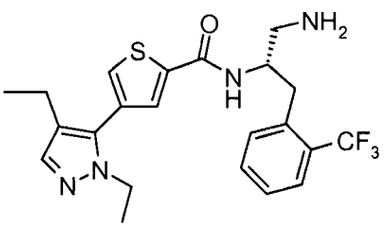


To a solution of methyl 4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (149 mg, 0.56 mmol) in THF/H_2O (5 mL/5 mL) was added KOH (158 mg, 2.82 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5mL x 3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly without of further purification: LC-MS (ES) m/z 251 $(M+H)^+$.

To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (315 mg, 0.68 mmol) in one portion,

followed by the addition of DIPEA (0.98 mL, 5.64 mmol) and 2-{(2S)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (196 mg, 0.56 mmol). After 2h, the solution was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (0.315 g, 94%) as a white solid: LC-MS (ES) m/z 581 $(M+H)^+$.

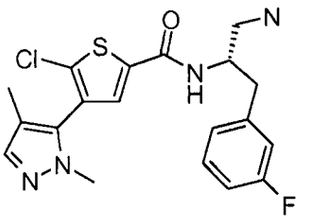
d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



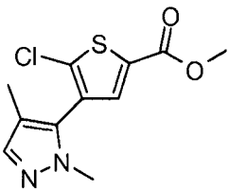
4-(1,4-diethyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (310 mg, 0.53 mmol) was dissolved in MeOH (1 mL) and was treated with NH_2NH_2 (0.34 mL, 10.68 mmol) . The reaction was stirred over 5 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water (2 mL) and ammonium hydroxide (3.47 mL, 30%, 26.7 mmol) was added. The mixture was extracted with DCM (5 mL x 3), dried over Na_2SO_4 and concentrated to give a free base of the tile compound. The free base was dissolved in MeOH (1 mL) and treated with HCl (4 M in dioxane, 2.1 mL). After stirring overnight, the reaction solution was concentrated to give the title compound (140 mg, 48%) as an off-white solid: LC-MS (ES) m/z 451 $(M+H)^+$, ^1H NMR (d_6-DMSO, 400 MHz) δ ppm 8.25-8.23 (m, 1H), 8.16-8.14 (m, 1H), 8.10-8.08 (m, 1H), 7.71-7.67 (m, 1H), 7.65-7.61 (m, 1H), 7.52-7.47 (m, 1H), 7.44-7.39 (m, 1H), 4.69 (m, 1H), 4.45-4.37 (m, 2H), 3.39-3.18 (m, 4H), 2.63-2.55 (m, 2H), 1.49-1.44 (m, 3H), and 1.24-1.19 (m, 3H).

Example 249

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



a) methyl 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



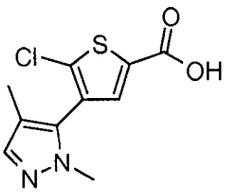
Method A:

To a solution of methyl 4-bromo-5-chloro-2-thiophenecarboxylate (500 mg, 1.96 mmol) in THF(10 mL) was added aqueous Na_2CO_3 (2N, 3mL, 6.0 mmol), $PdCl_2$(dppf) (143 mg, 0.196 mmol) and 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (522 mg, 2.35 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 10-20%) to afford the title compound (410 mg,77%) as a tan solid: LC-MS (ES) m/z 271 $(M+H)^+$.

Method B:

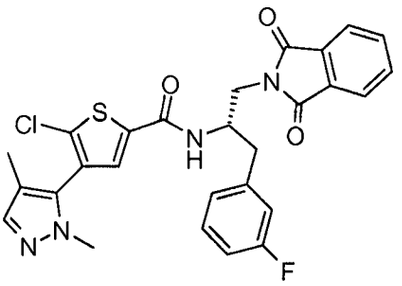
To a 250 mL sealed flask was added 1,4-dimethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (10.43 g, 47.0 mmol), potassium carbonate (16.23 g, 117 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (10 g, 39.1 mmol) and bis(tri-t-butylphosphine)palladium(0) (1.6 g, 3.13 mmol) in 1,4-dioxane (120 mL) and H_2O (20ml). After stirring for 90 min at 70 °C, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel (hexanes/EtOAC, 10-30%) to give the title compound (7.6 g, 72%) as a tan solid: LC-MS (ES) m/z 271 $(M+H)^+$.

b) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid



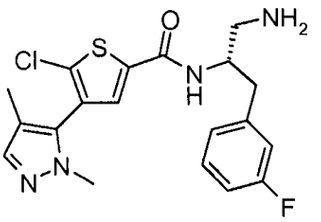
To a solution of methyl 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (7.6 g, 28.1 mmol) in THF/H_2O (30 mL/5 mL) was added KOH (4.72 g, 84 mmol). The reaction mixture was heated to 50 °C for 1 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (50 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid (6.8 g, 94%), which was used directly in the next step without further purification: LCMS (ES) m/z 257 $(M+H)^+$.

c) 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



To a 500 mL round-bottomed flask was added 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid (6.8 g, 26.5 mmol), 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (8.69 g, 29.1mmol), N,N-diisopropyl ethylamine (14 mL, 80 mmol) and Pybrop (18.52 g, 39.7 mmol) in dichloromethane (DCM) (100 mL). After stirring at RT for 1h, the reaction solution was washed with H_2O (2 x 100mL) and the organic layer was dried Na_2SO_4, filtered and concentrated. The crude product was added to a silica gel column and was eluted with (EtOAc/hexanes, 1:1) to give the title compound (6.1g, 42.9%) as a white solid: LCMS (ES) m/z 537 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

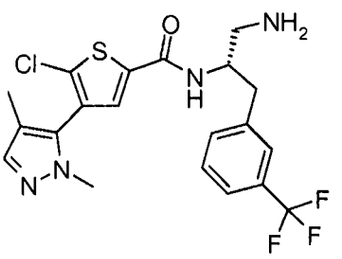


At RT, NH_2NH_2 (4 mL, 127 mmol) was added to 5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (5.2 g, 9.68 mmol) in MeOH (30 ml). After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (200 mL) and washed with H_2O (50 mL x 5).

To the above DCM solution was added HCl (36%, 50 mL, 600 mmol). After 1h, the aqueous phase was separated and washed with DCM (50 ml x 5). Water was removed under high vacuum to give the title compound (3.8 g, 79%) as a white solid: LC-MS (ES) m/z 407 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 8.75 (d, J = 8.8 Hz, 1H), 7.88 (s, 1H), 7.85 (m, 1H), 7.34-7.29 (m, 1H), 7.15-7.09 (m, 2H), 7.00-6.95 (m, 1H), 4.54 (m, 1H), 3.88 (s, 3H), 3.26-3.18 (m, 2H), 3.09-2.98 (m, 2H), and 2.08 (s, 3H).

Example 250

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

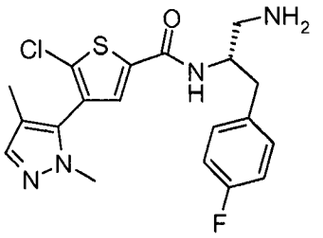


The title compound was prepared as a white solid (180 mg, 68%) according to the procedure of Example 249, except substituting 2-{(2S)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1H-isoindole-1,3(2H)-dione (209 mg, 0.6 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 457 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.94 (s, 1H), 7.90 (s, 1H), 7.65-

7.60 (m, 2H), 7.55-7.48 (m, 2H), 4.55 (m, 1), 3.89 (s, 3H), 3.37-3.27 (m, 2H), 3.16-3.06 (m, 2H), and 2.08 (s, 3H).

Example 251

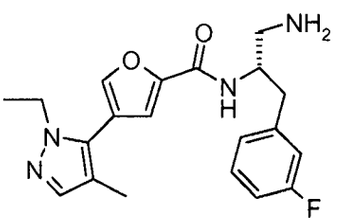
N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



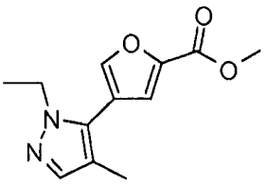
The title compound was prepared as white solid (95 mg, 39%) according to the procedure of Example 249, except substituting 2-[(2S)-2-amino-3-(4-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (584 mg, 1.96 mmol) for 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione: LC-MS (ES) m/z 407 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.81 (s, 2H), 7.35-7.31 (m, 2H), 7.06-7.01 (m, 2H), 4.51 (m, 1H), 3.89 (s, 3H), 3.25-3.16 (m, 2H), 3.05-2.94 (m, 2H), and 2.07 (s, 3H).

Example 252

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

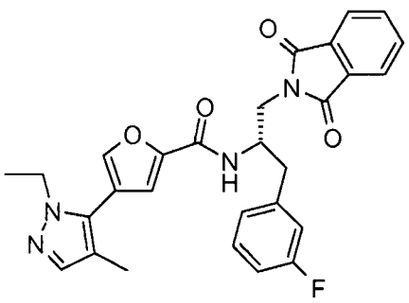


a) methyl 4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



To a solution of methyl 4-bromo-2-furancarboxylate (500 mg, 2.439 mmol) in THF (5 mL) was added aqueous Na_2CO_3 (2N, 3.6 mL, 7.2 mmol), $PdCl_2(dppf)$ (160 mg, 0.22 mmol), and 1-ethyl-4-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (700 mg, 2.96 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-40%) to afford the title compound (460 mg, 76 %) as a light yellow solid: LC-MS (ES) m/z 235 $(M+H)^+$.

b) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

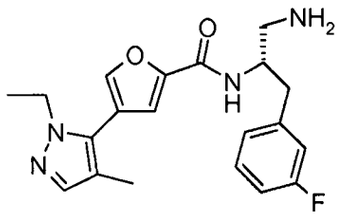


To a solution of methyl 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxylate (210 mg, 0.90 mmol) in THF/H_2O (5mL/0.5 mL) was added KOH (200 mg, 3.56 mmol). The reaction mixture was heated to 50 °C for 4 h. After the mixture was concentrated and diluted with H_2O (2 mL), the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly in the next step without further purification: LC-MS (ES) m/z 221 $(M+H)^+$.

To the crude 4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxylic acid in DCM (5 mL) at 25 °C was added PyBrOP (370 mg, 0.79 mmol) in one portion, followed by the addition of DIPEA (0.8 mL, 4.58 mmol). After 10 min, 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (220 mg, 0.74 mmol) was added to the reaction solution. After 2h, the reaction mixture was concentrated

and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (164 mg, 54%) as a white solid: LC-MS (ES) m/z 501 $(M+H)^+$.

c) *N*-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxamide

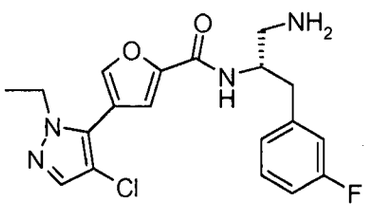


At RT, NH_2NH_2 (0.1 mL, 3.19 mmol) was added to a solution of N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-2-furancarboxamide (150 mg, 0.3 mmol) in MeOH (5 mL) . After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (10 mL) and washed with H_2O (10 mL x 3).

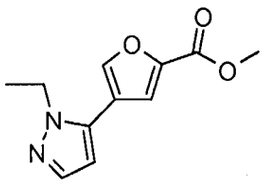
To the DCM solution was added HCl (36%, 1 mL, 12 mmol). After 1h, the aqueous phase was separated, and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (80 mg, 57%) as an off-white solid: LC-MS (ES) m/z 371 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 8.19 (s, 1H), 8.05 (s, 1H), 7.44 (s, 1H), 7.32 (m, 1H), 7.16-7.08 (m, 2H), 6.97 (m, 1H), 4.62 (m, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.38-3.18 (m, 2H), 3.10-2.99 (m, 2H), 2.15 (s, 3H), and 1.46 (t, J = 7.1 Hz, 3H).

Example 253

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

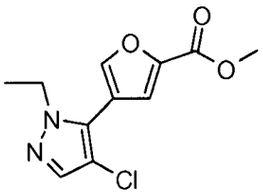


a) methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



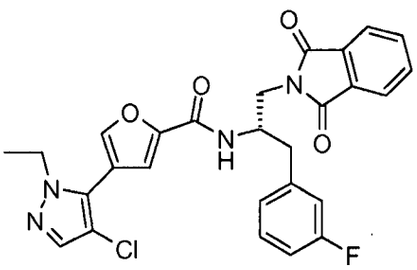
To a solution of methyl 4-bromo-2-furancarboxylate (1.0 g, 4.88 mmol) in THF (20 mL) was added aqueous Na_2CO_3 (2N, 8 mL, 16 mmoL), $PdCl_2$(dppf) (0.35 g, 0.49 mmol) and 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.3 g, 5.85 mmol). The reaction mixture was heated to 70° C in a sealed tube. After 2h, the reaction mixture was concentrated under vacuum and purified on silica (EtOAc/Hex, 20-40%) to afford the title compound (0.8 g, 74.5%) as a light yellow solid: LC-MS (ES) m/z = 221 $(M+H)^+$.

b) methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



A mixture of methyl 4-(1-ethyl-1H-pyrazol-5-yl)-2-furancarboxylate (300 mg, 1.36 mmol) and NCS (218 mg, 1.63 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. After 5h, the reaction mixture was concentrated and purified via column chromatography (silica, 10-20% EtOAc/Hexane) affording the title compound (260 mg, 75%) as a white solid: LC-MS (ES) m/z 255 $(M+H)^+$.

c) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-furancarboxamide

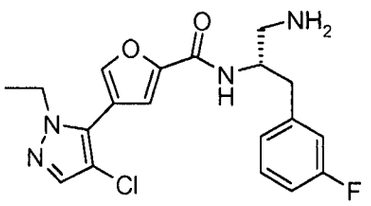


To a solution of methyl 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-2-furancarboxylate (250 mg, 0.98 mmol) in THF/H_2O (5mL/0.5 mL) was added KOH (200 mg, 3.56 mmol). The reaction mixture was heated to 50° C for 4 h. After the

mixture was concentrated and diluted with H_2O (2 mL), the pH was adjusted to 3. The mixture was extracted with DCM (5mL x3). The collected organic layers were concentrated under vacuum to give a crude acid, which was used directly without further purification: LC-MS (ES) m/z 241 $(M+H)^+$.

To the above crude acid in DCM (5 mL) at 25 °C was added PyBrOP (550 mg, 1.18 mmol) in one portion, followed by the addition of DIPEA (0.7 mL, 4.01 mmol). After 10 min, 2-[(2S)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (322 mg, 1.08 mmol) was added to the reaction solution. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 20-50 % EtOAc/Hexane) affording the title compound (360 mg, 70 %) as a white solid: LC-MS (ES) m/z 521 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

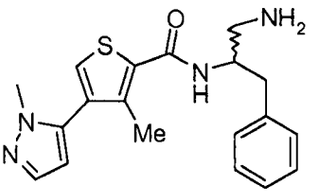


At RT, NH_2NH_2 (0.15 mL, 4.78 mmol) was added to a solution of 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-furancarboxamide (350 mg, 0.67 mmol) in MeOH (5 mL) . After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (15 mL) and washed with H_2O (10 mL x 3).

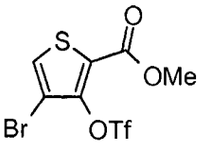
To the above DCM solution was added HCl (36%, 2 mL, 23.7 mmol)). After 1h, the aqueous phase was separated and washed with DCM (10 ml x 3). Water was removed under high vacuum to give the title compound (260 mg, 78%) as an off-white solid: LC-MS (ES) m/z 391 $(M+H)^+$. NMR (d_6-DMSO, 400 MHz) δ ppm 8.70 (m, 1H), 8.29 (s, 1H), 8.02 (m, 2H), 7.70 (s, 1H), 7.50-7.45 (m, 1H), 7.36-7.30 (m, 1H), 7.14-7.08 (m, 2H), 7.06-7.01 (m, 1H), 4.43 (m, 1H), 4.16 (q, J = 7.3 Hz, 2H), 3.04-2.88 (m, 4H), and 1.30 (t, J = 7.3 Hz, 3H).

Example 254

N-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

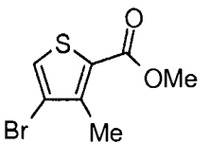


a) methyl 4-bromo-3-{[(trifluoromethyl)sulfonyl]oxy}-2-thiophenecarboxylate



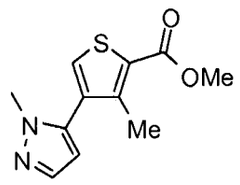
To a solution of methyl 4-bromo-3-{[(trifluoromethyl)sulfonyl]oxy}-2-thiophenecarboxylate (0.948 g, 4.0 mmol) in CH_2Cl_2 (5 mL) and pyridine (1 mL) at 0 °C was added Tf_2O (1.0 mL, 6.0 mmol). The mixture was stirred for 1 h, poured onto ice water (10 mL) and extracted with CH_2Cl_2 (5 mL x 3). The collected organic layers were dried (Na_2SO_4) and concentrated to give a red syrup which was used directly in the next step without further purification: LC-MS (ES) m/z 370 $(M+H)^+$.

b) methyl 4-bromo-3-methyl-2-thiophenecarboxylate



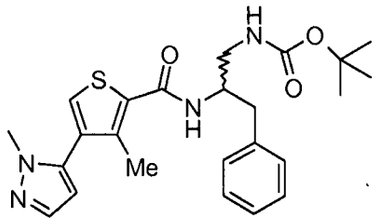
To a solution of methyl 4-bromo-3-{[(trifluoromethyl)sulfonyl]oxy}-2-thiophenecarboxylate (825 mg, 2.25 mmol) in dioxane/H_2O (5 mL/1 mL) was added K_2CO_3 (930 mg, 6.75 mmol), tetrakistriphenylphosphine Pd(0) (260 mg, 0.22 mmol), and methylboronic acid (175 mg, 2.91 mmol). The reaction mixture was heated to 70° C in a sealed tube for 12h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 9:1) to give the title compound (441 mg, 84%) as a brown solid: LC-MS (ES) m/z 236 $(M+H)^+$.

c) methyl 4-[1-(dimethylamino)ethenyl]-3-methyl-2-thiophenecarboxylate



To a solution of methyl 4-bromo-3-methyl-2-thiophenecarboxylate (300 mg, 1.27 mmol) in dioxane/H_2O (5 mL/1 mL) was added K_2CO_3 (525 mg, 3.80 mmol), tetrakistriphenylphosphine Pd(0) (15 mg, 0.01 mmol), and 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (345 mg,1.7 mmol). The reaction mixture was heated to 70 °C in a sealed tube for 2h. The reaction solution was concentrated under vacuum and purified on silica gel (hexanes/EtOAc, 9:1 to 4:1) to give the title compound (270mg, 90%): LC-MS (ES) m/z 237 $(M+H)^+$.

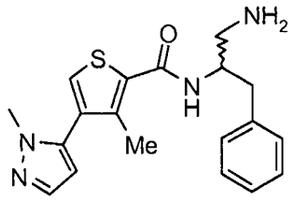
d) 1,1-dimethylethyl [2-({[3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



To a solution of methyl 4-[1-(dimethylamino)ethenyl]-3-methyl-2-thiophenecarboxylate (50 mg, 0.21 mmol) in THF/H_2O (2 mL/0.5 mL) was added KOH (122 mg, 2.1 mmol). The resulting mixture was heated to 50 °C for 2h. The THF was removed under vacuum and the aqueous layer was acidified with 6 N HCl to pH 3 and extracted with CH_2Cl_2 (5 mL x 3). The organic fractions was dried over Na_2SO_4 and concentrated to give the crude 3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid, which was used directly in the next step.

To a solution of the crude 3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylic acid in DCM (2 mL) was added PyBrop (0.14 g, 0.3 mmol) and DIPEA (0.1 mL, 0.57 mmol). After 15 min, 1,1-dimethylethyl (2-amino-3-phenylpropyl)carbamate was added to the reaction in one portion and stirred for 2h at RT. The reaction solution was concentrated under vacuum and purified on silica gel (EtOAc /Hexane, 20-50%) to give the title compound (51 mg, 49 % for two steps) as a solid: LC-MS (ES) m/z 455 $(M+H)^+$.

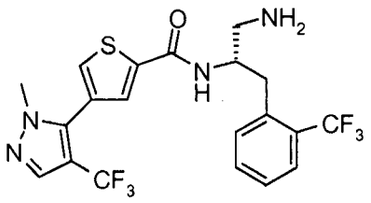
e) *N*-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



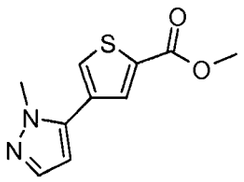
To a solution of 1,1-dimethylethyl [2-({[3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (51 mg, 0.11 mmol) in DCM (1 mL) was added TFA (1 mL). The reaction was stirred over 5h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-10 %) to afford the bis-TFA salt of the title compound. (16 mg, 41%): LC-MS (ES) m/z 355 $(M+H)^+$. NMR (d_4-MeOD, 400 MHz) δ ppm 7.64 (s, 1H), 7.56 (d, J = 1.8 Hz, 1H), 7.36-7.30 (m, 4H), 7.28-7.21 (m, 1H), 6.30 (d, J = 2.0 Hz, 1H), 4.58 (m, 1H), 3.69 (s, 3H), 3.27-3.13 (m, 2H), 3.07-2.93 (m, 2H), and 2.13 (s, 3H).

Example 255

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide



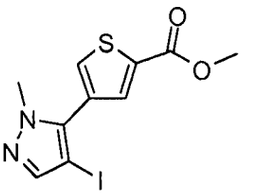
a) methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (1.0 g, 4.5 mmol) in dioxane/H_2O (5:1, 12 mL) was added K_2CO_3 (1.86 mg, 13.5 mmol), tetrakistriphenylphosphine Pd(0) (300 mg, 0.25 mmol), and 1-methyl-5-(4,4,5,5-

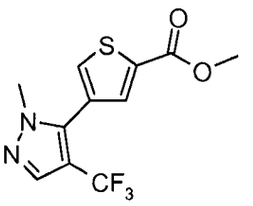
tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (1.23 g, 5.9 mmol). The reaction mixture was heated to 75° C in a sealed tube for 2h. The reaction mixture was concentrated and purified on silica gel (EtOAc/Hex 10-40%) to give the title compound (701 mg, 70%) as a white solid: LC-MS (ES) m/z 223 $(M+H)^+$.

b) methyl 4-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



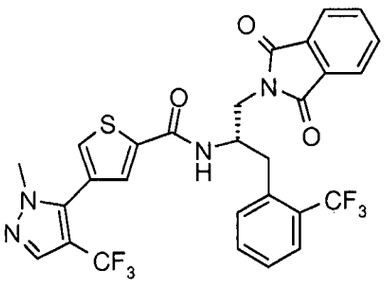
To a solution of methyl 4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (700 m g, 3.15 mmol) in THF (5 mL) was added NIS (922 mg, 4.09 mmol) in one portion. The reaction mixture was stirred at 75 °C for 10 h, and then cooled to room temperature. The reaction mixture was concentrated and purified on silica gel (EtOAc/Hex 10-20%) to give the title compound (470 mg, 43%) as an off white solid: LC-MS (ES) m/z 350 $(M+H)^+$.

c) methyl 4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxylate



To a solution of methyl 4-(4-iodo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (470 mg, 1.35 mmol), copper (I) iodide (256 mg, 1.35 mmol) and potassium fluoride (78 mg, 1.35 mmol) in anhydrous DMF/HMPA (2 ml/2 mL) was added triethyl(trifluoromethyl)silane (745 mg, 4.04 mmol). The mixture was heated to 70 °C under N_2 in a sealed tube. After 10h, the reaction was quenched with NH_4Cl (sat'd) (2 mL), extracted with ether (5 mL x 5) and washed with distilled water (5 mL x 5). The combined organic phase was dried over Mg_2SO_4 and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (0.29 g, 74%) as a yellow syrup: LC-MS (ES) m/z 291 $(M+H)^+$.

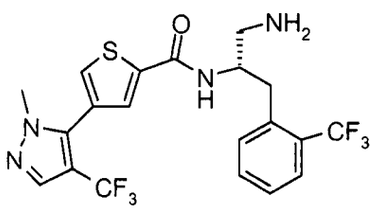
d) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide



To a solution of methyl 4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxylate (150 mg, 0.52 mmol) in THF/H_2O (2 mL/0.5 mL) was added KOH (116 mg, 2.0 mmol). The reaction mixture was heated to 50 °C for 2 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid, which was used directly in the next step without further purification: LC-MS (ES) m/z 277 $(M+H)^+$.

To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (279 mg, 0.59 mmol) in one portion, followed by the addition of DIPEA (0.5 mL, 2.87 mmol) and 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (174 mg, 0.5 mmol). After 2h, the solution was concentrated and purified via column chromatography (silica, 1-10 % MeOH/$CHCl_3$) affording the title compound (0.21 g, 67% for 2 steps): LC-MS (ES) m/z 607 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide



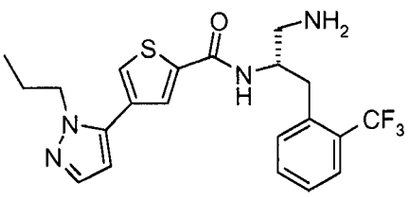
N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide (210 mg, 0.35 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.5 mL, 15.9 mmol). The reaction was stirred over 10 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 40-

446

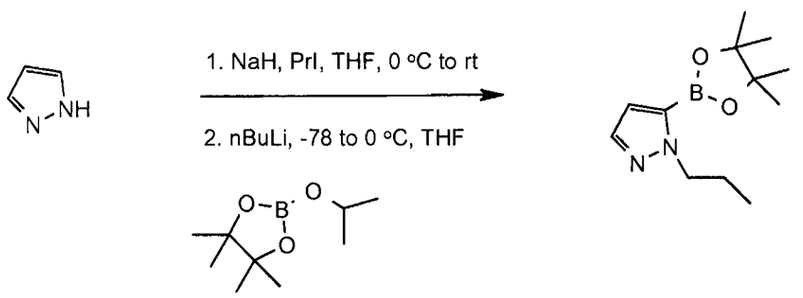
10%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water, and neutralized with ammonium hydroxide. The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH and treated with HCl (aq). After stirring overnight, the reaction was concentrated to give the title compound (95 mg, 57%) as a white solid. LC-MS: LC-MS (ES) m/z 477 $(M+H)^+$. NMR (d_6-DMSO, 400 MHz): δ ppm 8.92 (d, J = 9.1 Hz, 1H), 8.06 (m, 4H), 7.99 (s, 1H), 7.69 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 1H), 7.53 (m, 1H), 7.43 (m, 1H), 4.49 (m, 1H), 3.83 (s, 3H), and 3.14-2.99 (m, 4H).

Example 256

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide



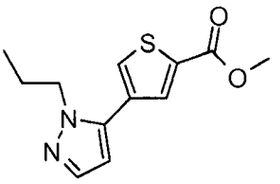
a) 1-propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole



To a suspension of NaH (60% in mineral oil, 4.0 g, 100 mmol) in THF (200 mL) was added 1H-pyrazole (6.8 g, 100 mmol) at 0 °C portionwise. After stirring at RT for 1h, PrI (17.85 g, 105 mmol) was added dropwise at 0 °C. The reaction mixture was stirred for 10h and monitored by LC-MS: m/e = 111 $(M+H)^+$. After the reaction was complete, NaI was removed by filtration. The resulting 1-propyl-1*H*-pyrazole containing THF solution was used directly in the next step.

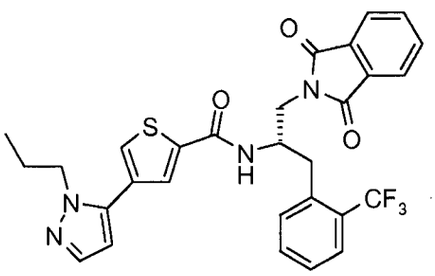
To the above THF solution of 1-propyl-1*H*-pyrazole was added n-BuLi (2.5M in Hexane, 40 mL, 100 mmol) at -78°C,. The reaction solution was stirred for 2 hours at RT and then re-cooled to -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. To the reaction solution was added 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (18.6 g, 100 mmol). After 30 min at -78°C, the reaction was quenched with saturated NH_4Cl solution and extracted with DCM. The organics were dried over Na_2SO_4 and concentrated under vacuum to afford the title compound as a brown solid which was used directly without further purification: LC-MS (ES) m/z 154 $(M+H)^+$ for [RB(OH)2].

b) methyl 4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



To a solution of methyl 4-bromo-2-thiophenecarboxylate (221 mg, 1.0 mmol) in dioxane/H_2O (5:1, 6 mL) was added K_2CO_3 (414 mg, 3.0 mmol), tetrakistriphenylphosphine Pd(0) (60 mg, 0.05 mmol), and 1-propyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole (404 mg, 1.5 mmol). The reaction mixture was heated to 70° C in a sealed tube for 2h. The reaction mixture was concentrated and purified on silica gel (EtOAc/Hex 10-40%) to give the title compound (176 mg, 70%) as a white solid: LC-MS (ES) m/z 251 $(M+H)^+$.

c) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

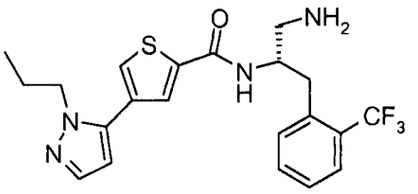


To a solution of methyl 4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate

(160 mg, 0.64 mmol) in THF/H_2O (2 mL/1 mL) was added KOH (151 mg, 2.56 mmol). The reaction mixture was heated to 50 °C for 2 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid, which was used directly in the next step without further purification. LCMS (ES) m/z = 237 $(M+H)^+$.

To the above acid in DCM (2 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (298 mg, 0.64 mmol) in one portion, followed by the addition of DIPEA (0.2 mL, 1.15 mmol) and 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (208 mg, 0.6 mmol). After 1h, the solution was concentrated and purified via column chromatography (silica, 1-10 % MeOH/$CHCl_3$) affording the title compound (0.22 g, 61% for 2 steps): LC-MS (ES) m/z 567 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

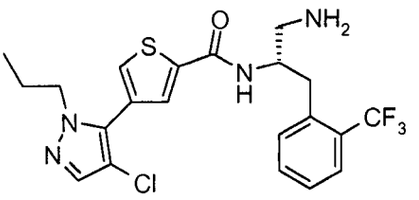


N-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (220 mg, 0.36 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.3 mL, 9.56 mmol). The reaction was stirred over 10 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water and neutralized with ammonium hydroxide. The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated to give a free base of the title compound. The free base compound was dissolved in MeOH (2 mL) and treated with HCl (4M in dioxane). After stirring overnight, the reaction solution was concentrated to give the title compound (112 mg, 57%) as an off white solid: LC-MS (ES) m/z 437 $(M+H)^+$, NMR (d_6-DMSO, 400 MHz): δ ppm 9.06-8.99 (m, 1H), 8.23-8.02 (m, 4H), 7.92 (br s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.62-7.49 (m, 3H), 7.42 (m,

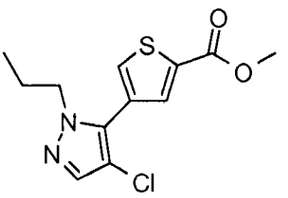
1H), 4.50 (m, 1H), 4.20 (m, 2H), 3.15-2.99 (m, 4H), 1.74 (m, 2H), and 0.80 (t, J = 7.3 Hz, 3H).

Example 257

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

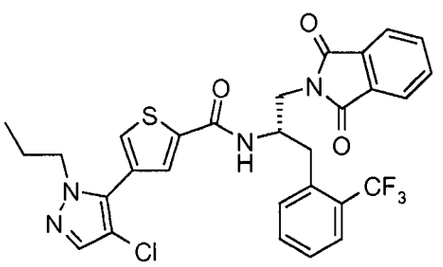


a) methyl 4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



A mixture of methyl 4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (250 mg, 1.0 mmol) and NCS (200 mg, 1.5 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 10% EtOAc/Hexane) affording the title compound (199 mg, 70%) as a white solid: LC-MS (ES) m/z 285 $(M+H)^+$.

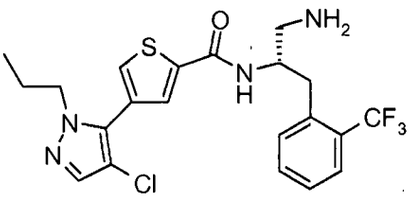
b) 4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide



To a solution of methyl 4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate (199 mg, 0.7 mmol) in THF/H_2O (2 mL/0.5 mL) was added KOH (100 mg, 1.7 mmol). The reaction mixture was heated to 50 °C for 2 h. After the mixture was concentrated and diluted with H_2O, the pH was adjusted to 3. The mixture was extracted with DCM (5 mL x 3). The collected organic layers were concentrated under vacuum to give the crude acid, which was used directly in the next step without further purification: LC-MS (ES) m/z 271 $(M+H)^+$.

To the above acid in DCM (5 mL) at 25 °C was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate (PyBrOP) (326 mg, 0.7 mmol) in one portion, followed by the addition of DIPEA (0.3 mL, 1.15 mmol) and 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (232 mg, 0.7 mmol). After 10 min, the solution was concentrated and purified via column chromatography (silica, 1-10 % MeOH/$CHCl_3$) affording the title compound (312 mg, 74% for 2 steps): LC-MS (ES) m/z 601 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

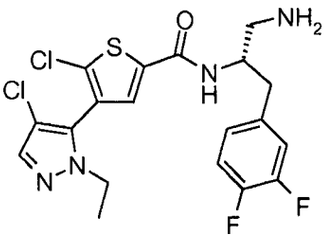


4-(4-Chloro-1-propyl-1*H*-pyrazol-5-yl)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-2-thiophenecarboxamide (312 mg, 0.52 mmol) was dissolved in MeOH (2 mL) and was treated with NH_2NH_2 (0.5 mL, 15.9 mmol). The reaction was stirred over 10 h, concentrated and purified by reverse-phase HPLC (C18 column: H_2O/CH_3CN, 95-5%) to afford the bis-TFA salt of the title compound. The bis-TFA salt was dissovled in water and neutralized with ammonium hydroxide. The mixture was extracted with DCM, dried over Na_2SO_4, and concentrated to give a free base of the tile compound. The free base compound was dissolved in MeOH (2 mL) and treated with HCl (aq). After stirring overnight, the reaction was concentrated to give the title compound (185 mg, 66%) as an off white solid: LC-MS (ES) m/z 471 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.92 (m, 2H), 7.74-7.68 (m, 1H), 7.60 (s, 1H), 7.58-7.51 (m, 2H), 7.45-7.41 (m,

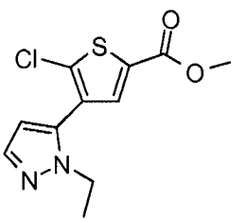
1H), 4.67 (m, 1H), 4.15 (t, J = 7.1 Hz, 2H), 3.37-3.09 (m, 4H), 1.77 (m, 2H), and 0.82 (t, J = 7.6 Hz, 3H).

Example 258

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

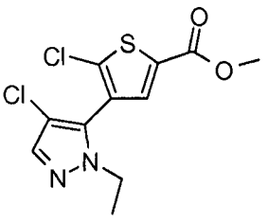


a) methyl 5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



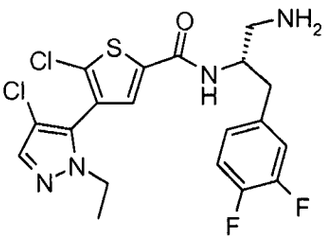
To a 100 mL sealed flask was added 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.61 g, 11.74 mmol), potassium carbonate (3.25 g, 23.48 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (2 g, 7.83 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.4 g, 0.78 mmol) in 1,2-dimethoxyethane (DME) (50 mL) and H_2O (10 ml). After stirring for 3h at 70 °C, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [EtOAc/hexanes, 10-30%] to give the product [1.8 g, 85%] as an off white solid: LC-MS (ES) m/z 271 $(M+H)^+$.

b) methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxylate



Methyl 5-chloro-4-(1-ethyl-1H-pyrazol-5-yl)-2-thiophenecarboxylate (1.8 g, 6.65 mmol) and NCS (1.3 g, 9.74 mmol) in THF (10 mL) were heated to 70 °C under N_2 for 2 h. The reaction solution was concentrated and purified on silica (EtOAc/Hex, 10-30%) to afford the title compound (1.5 g, 74%) as a syrup: LC-MS (ES) m/z 305 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

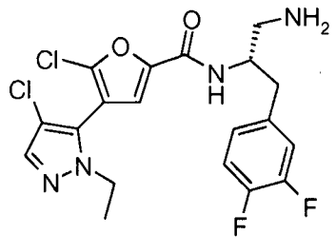


The title compound (290 mg, 58.4 %) was prepared as an off-white solid according to the procedure of Example 236, except substituting 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-thiophenecarboxamide (526 mg, 1.662 mmol) for 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide: LC-MS (ES) m/z 459 $(M+H)^+$,
NMR (d_4-MeOD, 400 MHz) δ ppm 7.76 (m, 1H), 7.62 (s, 1H), 7.28-7.22 (m, 1H), 7.20-7.10 (m, 2H), 4.52 (m, 1H), 4.07 (m, 2H), 3.27-3.16 (m 2H), 3.05-2.94 (m, 2H), and 1.34 (m, 3H).

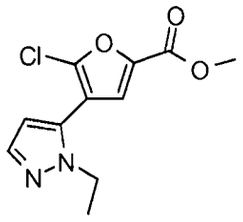
Example 259

453

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide

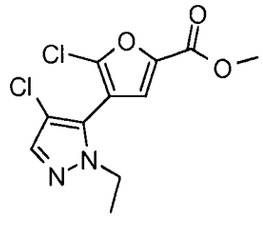


a) methyl 5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



To a 100 mL sealed flask was added 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.61 g, 11.74 mmol), potassium carbonate (3.25 g, 23.48 mmol), methyl 4-bromo-5-chloro-2-furancarboxylate (1.85 g, 8.33 mmol) and bis(tri-t-butylphosphine)palladium(0) (0.16 g, 0.31 mmol) in 1,2-Dimethoxyethane (DME) (30 mL) and H_2O (5 mL). After stirring for 2h at 75 °C, the reaction solution was diluted with DCM (100 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [EtOAc/hexanes, 10-30%] to give the product (0.8 g, 50.1%) as an off-white solid: LC-MS (ES) m/z 255 $(M+H)^+$.

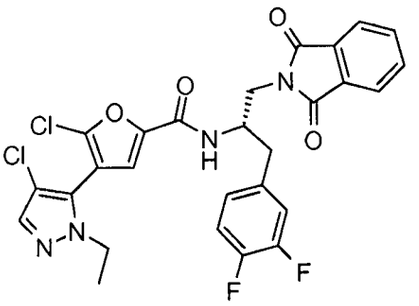
b) methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate



A mixture of methyl 5-chloro-4-(1-ethyl-1H-pyrazol-5-yl)-2-furancarboxylate (800 mg, 3.14 mmol) and NCS (600 mg, 4.49 mmol) in THF (5 mL) was heated to 70 °C in a sealed tube. After 2h, the reaction mixture was concentrated and purified

via column chromatography (silica, 10-20% EtOAc/Hexane) affording the title compound (710 mg, 78%) as a white solid: LC-MS (ES) m/z 289 $(M+H)^+$.

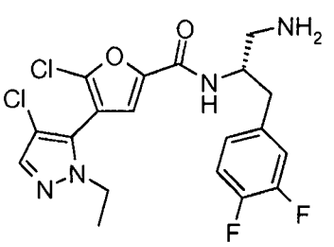
c) 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide



To a solution of methyl 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxylate (480 mg, 1.66 mmol) in THF/H_2O (5mL/1 mL) was added KOH (460 mg, 8.20 mmol). The reaction mixture was heated to 50° C for 4 h. After the mixture was concentrated and diluted with H_2O (2 mL), the pH was adjusted to 3. The mixture was extracted with DCM (10 mL x3). The collected organic layers were concentrated under vacuum to give a crude acid (420 mg, 92%), which was used directly without further purification: LC-MS (ES) m/z 275 $(M+H)^+$.

To the above acid (400 mg) in DCM (5 mL) at 25 °C was added PyBrOP (881 mg, 1.89 mmol) in one portion, followed by the addition of DIPEA (1.5 mL, 8.59 mmol). After 10 min, 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (506 mg, 1.60 mmol) was added. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 30-50 % EtOAc/Hexane) affording the title compound (655 mg, 79%) as a white solid: LC-MS (ES) m/z 573 $(M+H)^+$.

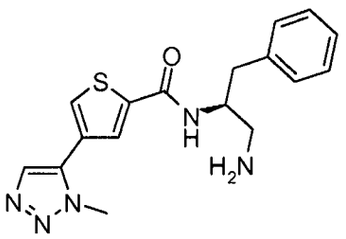
c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide



At RT, NH_2NH_2 (0.5 mL, 15.93 mmol) was added to a solution of 5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-2-furancarboxamide (610 mg, 1.06 mmol) in MeOH (5 mL). After 10h, the solvent was removed under vacuum. The resulting residue was taken into DCM (20 mL) and washed with H_2O (20 mL x 3).

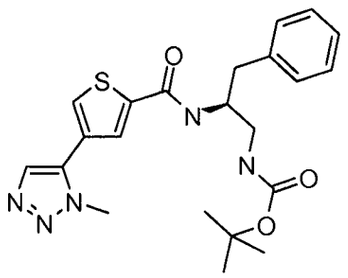
To the DCM solution was added HCl (36%, 10 mL, 120 mmol). After 1h, the aqueous phase was separated and washed with DCM (30 ml x 3). Water was removed under high vacuum to give the tilte compound (410 mg, 87%) as an off-white solid: LC-MS (ES) m/z 443 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.61 (s, 1H), 7.36 (s, 1H), 7.29-7.10 (m, 3H), 4.57 (m, 1H), 4.09 (q, J = 7.3 Hz, 2H), 3.27-3.23 (m, 1H), 3.20-3.14 (m, 1H), 3.06-3.01 (m, 1H), 2.97-2.92 (m, 1H), and 1.36 (t, J = 7.3 Hz, 3H).

Example 260



Preparation of N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



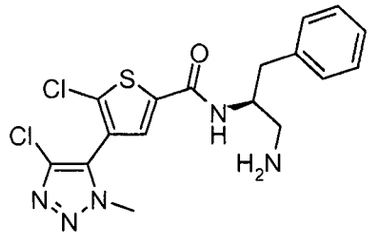
A mixture of 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (prepared according to Preparation 22 except substituting

2-[(2S)-2-amino-3-phenylpropyl]-1H-isoindole-1,3(2H)-dione for 2-[(2S)-2-amino-3-(2,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione) (236 mg, 0.537 mmol), 1-methyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole (200 mg, 0.537 mmol) (prepared according to patent IPN WO97/01553), $Pd(PPh_3)_2Cl_2$ (37.7 mg, 0.054 mmol), TRIETHYLAMINE (74.9 µl, 0.537 mmol) and toluene (3 ml) was degassed by N_2 and sealed. The reaction mixture was heated at 110 °C for 4 hr. LC/MS showed the reaction was completed. The reaction mixture was concentrated and purified *via* column chromatography (silica, 70% EtOAc in hexane) to give the title product (120 mg, 51%) LCMS (ES) m/z = 442.2 (M+H)

b) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

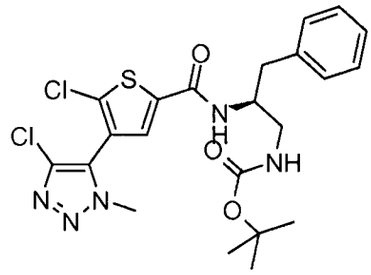
A solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (60 mg, 0.14 mmol) in TFA-DCM (4ml, 1:3) was stirred at rt for 1h. LCMS showed the reaction was completed. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC (5%-65% acetonitrile in water with 0.1% TFA) to give 42.2 mg (67%) of the TFA salt as a white solid. LCMS (ES) m/z 342.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.52 Hz, 1H), 7.87-7.91 (m, 2H), 7.34-7.21 (m, 5H), 4.55 (m, 1H), 4.19 (s, 3H), 3.30-3.21 (m, 1H), 3.09-3.18 (m, 1H), 3.01 (d, J=7.6Hz, 2H)

Example 261



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-Dimethylethyl [(2*S*)-2-({[5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol- 5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

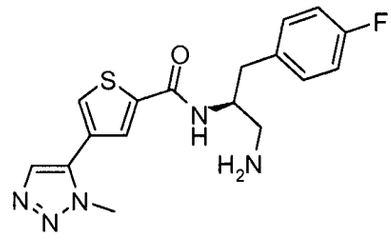


To a solution of 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (70 mg, 0.16 mmol) in 2 ml of DMF was added NCS (42.3 mg, 0.32 mmol). The reaction mixture was heated at 50 °C for 2 hr and then diluted with 50 ml of EtOAc. The organic layer was washed with H_2O and concentrated to give the title product as a crude mixture, which was used in next step without purification. LCMS (ES) m/z = 510.2 (M+H)

b) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (crude from a) in TFA-DCM (4ml, 1:3) was stirred at rt for 1h. The reaction mixture was concentrated and the residue was purified by reverse phase HPLC (5%-65% acetonitrile in water with 0.1% TFA) to give 10 mg (12% two steps) of white solid as TFA salt. LCMS (ES) m/z 410.0/412.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.62 (s, 1H), 7.32-7.25 (m, 5H), 4.55 (m, 1H), 4.02 (s, 3H), 3.21 (m, 1H), 3.10 (m, 1H), 2.98 (d, 2H).

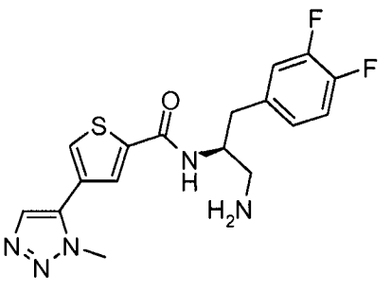
Example 262



Preparation of N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

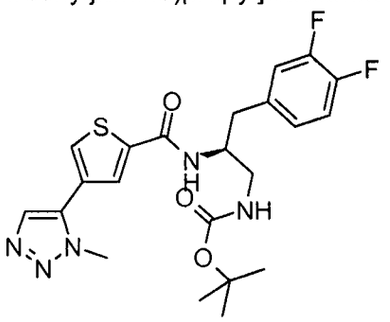
The title compound was prepared as a white solid according to the procedure of Example 260, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-fluorophenyl)propyl]carbamate (123mg, 0.27mmol) for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LCMS (ES) m/z 360.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.05 (d, J=1.6 Hz, 1H), 7.89-7.91 (m, 2H), 7.33-7.30 (m, 2H, 7.06-7.02 (m, 2H), 4.55 (m, 1H), 4.20 (s, 3H), 3.23 (m, 1H), 3.17 (m, 1H), 2.99 (m, 2H).

Example 263



Preparation of N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-Dimethylethyl [(2*S*)-3-(3,4-difluorophenyl)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)propyl]carbamate



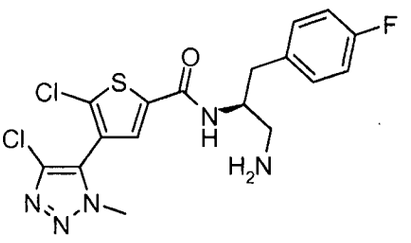
A solution of 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-di-fluorophenyl)propyl]carbamate (50 mg, 0.11 mmol), 1-methyl-5-(4,4,5,5-

tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-1,2,3-triazole (44 mg, 0.21 mmol) , Na_2CO_3 (2N, 0.1ml) and $PddppfCl_2$ (8.6 mg, 0.01 mmol) in 3 ml of 1,4-dioxane was irridiated in MW reactor at 150 °C for 20 min. The crude reaction mixture was purified by column chromatography (silica, 70% EtOAc in hexane) to give the title product (29 mg, 46%): LCMS (ES) m/z = 478.2 (M+H).

b) *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared according to Example 260 b) except substituting 1,1-dimethylethyl [(2*S*)-3-(3,4-difluorophenyl)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)propyl]carbamate (29mg, 0.06mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 378.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.07 (d, J=1.6 Hz, 1H), 7.88-7.91 (m, 2H), 7.23-7.09 (m, 3H), 4.55 (m, 1H), 4.20 (s, 3H), 3.24 (m, 1H), 3.15 (m, 1H), 2.98 (m, 2H).

Example 264

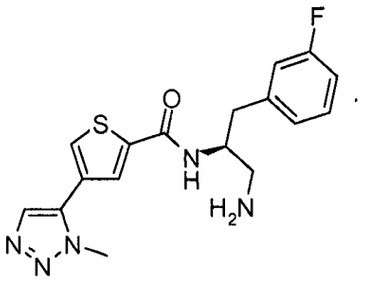


Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-(4-fluorophenyl)propyl]carbamate (68 mg, 0.15 mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 428.0/430.0 $(M+H)^+$, 1H NMR (400 MHz,

METHANOL-*d*4) δppm 7.66 (s, 1H), 7.30 (m, 2H), 7.04 (m, 2H), 4.55 (m, 1H), 4.02 (s, 3H, 3.21-3.10 (m, 2H), 2.98 (m, 2H).

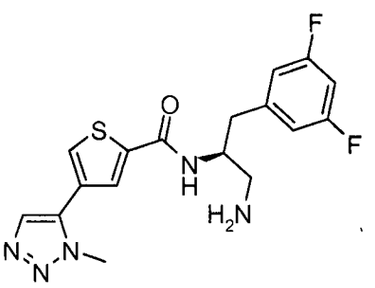
Example 265



Preparation *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3-fluorophenyl)propyl]carbamate (300mg, 0.66mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 360.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.6 Hz, 1H), 7.90 (m, 2H), 7.33-7.30 (m, 1H), 7.13-7.09 (m, 2H), 6.98-6.95 (m, 1H), 4.55 (m, 1H), 4.19 (s, 3H), 3.24 (m, 1H), 3.17 (m, 1H), 3.04-2.99 (m, 2H).

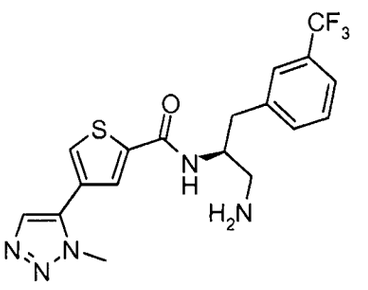
Example 266



Preparation *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,5-difluorophenyl)propyl]carbamate (300mg, 0.66mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 378.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.6 Hz, 1H), 7.91 (m, 2H), 6.96-6.93 (m, 2H), 6.84-6.83 (m, 1H), 4.55 (m, 1H), 4.19 (s, 3H), 3.24 (m, 1H), 3.19 (m, 1H), 3.05-2.98 (m, 2H).

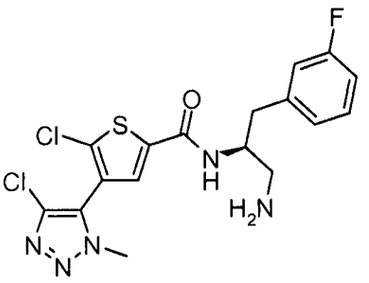
Example 267



Preparation *N*-{(1*S*)-2-amino-1-[(3-trifluoromethylphenyl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3-(trifluoromethyl)phenyl)propyl]carbamate (500 mg, 0.99 mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 410.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.06 (d, J=1.2 Hz, 1H), 7.97 (s, 1H), 7.91 (s, 1H), 7.72 (d, J=1.2Hz, 1H) 7.54 (m, 2H), 7.44 (m, 1H), 4.55 (m, 1H), 4.21 (s, 3H), 3.30-3.10 (m, 4H).

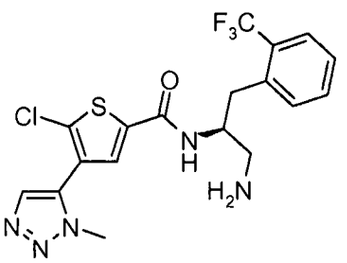
Example 268



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

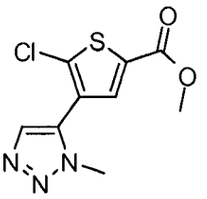
The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-(3-fluorophenyl)propyl]carbamate (50mg, 0.11mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 428.0/430.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.63 (s, 1H), 7.33 (m, 1H), 7.12-7.07 (m, 3H), 4.55 (m, 1H), 4.02 (s, 3H), 3.23-2.98 (m, 4H).

Example 269



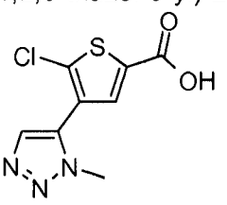
Preparation of N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) methyl 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate



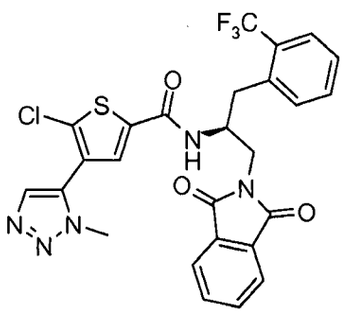
A mixture of 1-methyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole (2.0 g, 5.37 mmol), methyl 4-bromo-5-chloro-2-thiophenecarboxylate (1.25 g, 4.9 mmol), $Pd(PPh_3)_2Cl_2$ (171 mg, 0.244 mmol), TRIETHYLAMINE (0.68 ml, 4.89 mmol) and toluene (3 ml) was heated at 110 °C for 4hr under N_2. The reaction mixture was purified *via* column chromatography (silica, 50%-70% EtOAc in hexane) to give the title compound as a white solid (400 mg, 32%): LCMS (ES) m/z 258.2 $(M+H)^+$.

b) 5-Chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid



A solution of methyl 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate (400 mg, 1.55 mmol) and 1N LiOH (2.0 ml, 2.0 mmol) in THF (6 ml) was stirred at rt overnight. After removal of THF, the residue was diluted with 10 ml of H_2O and washed with DCM (10ml x 2). The aqueous layer was acidified to pH 3 with 1N HCl and then extracted with EtOAc (30 ml x 4). The organic layers were combined and concentrated to give 370 mg of the title compound as a white solid. LCMS (ES) m/z 244.0 $(M+H)^+$

c) 5-Chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

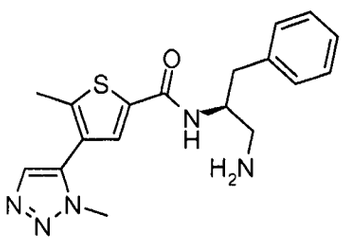


A solution of 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid (370mg, 1.52mmol), 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione (from Preparation 6, 529mg, 1.52 mmol), PyBrop (708 mg, 1.52 mmol) and DIPEA (2.65 ml, 15.2 mmol) in 20 ml of DCM was stirred at rt for 2hr. The reaction mixture was diluted with 50 ml of DCM and washed with H_2O, 0.1N HCl and brine. The organic layer was concentrated and the residue was purified *via* column chromatography (silica, 50%-70% EtOAc in hexane) to give the title compound as a white solid (700mg, 80%): LCMS (ES) m/z 574.0 $(M+H)^+$.

d) N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

A solution of 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide (700 mg, 1.22 mmol) and hydrazine (0.19 mL, 6.1 mmol) in 5 mL of MeOH was stirred at rt overnight, diluted with 200 ml of H_2O and extracted with DCM (100 ml x2). The combined organic layers were concentrated and the resulting solid was dissolved in 6N HCl (50 ml). The aqueous layer was washed with DCM (50 ml x2). The organic layers were discarded and the remaining aqueous solution was concentrated to give the product as an HCl salt (490mg, 75%): LCMS (ES) m/z 444.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.10(m, 1H), 7.92 (m, 1H), 7.73 (m, 1H), 7.57 (m, 1H), 7.44 (m, 1H), 4.65 (m, 1H), 4.17 (s, 3H), 3.25-3.11 (m, 4H).

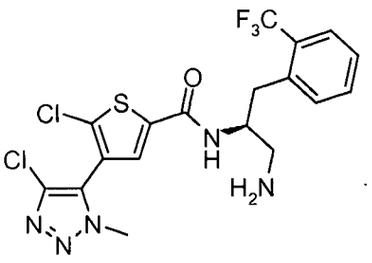
Example 270



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 269, except substituting methyl 4-bromo-5-methyl-2-thiophenecarboxylate (from Preparation 10) for methyl 4-bromo-5-chloro-2-thiophenecarboxylate and 2-{(2*S*)-2-amino-3-phenylpropyl}-1*H*-isoindole-1,3(2*H*)-dione (preparation 5) for 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 356.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.60 (s, 1H), 8.01(s, 1H), 7.34-7.21 (m, 5H), 4.55 (m, 1H), 4.26 (s, 3H), 3.25 (m, 2H), 3.03 (m, 2H), 2.21 (s, 3H).

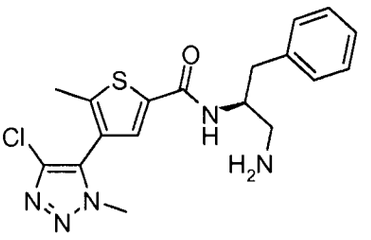
Example 271



Preparation of N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting N-{(1S)-2-amino-1-[(2-(trifluoromethyl)phenyl) methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide (120 mg, 0.27 mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 478.0/ 480.0$(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.79 (s, 1H), 7.73(d, J=7.6Hz, 1H), 7.56 (m, 2H), 7.45 (m, 1H), 4.65 (m, 1H), 4.05 (s, 3H), 3.29-3.10 (m, 4H).

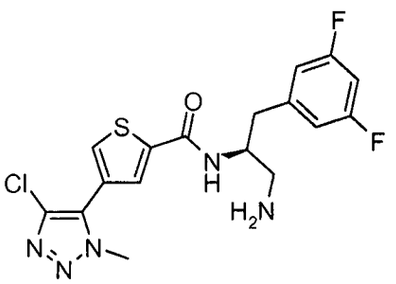
Example 272



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide

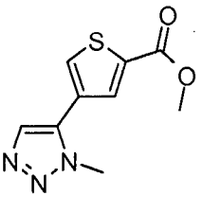
The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (prepared in Example 270) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 390.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.72(s, 1H), 7.31-7.22 (m, 5H), 4.55 (m, 1H), 3.99 (s, 3H), 3.19 (m, 2H), 3.02 (m, 2H), 2.41 (s, 3H).

Example 273



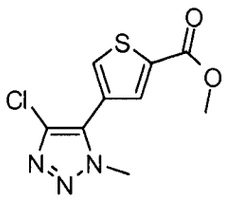
Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) Methyl 4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate



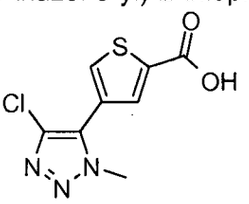
The title compound was prepared according to the procedure of Example 269 a), except substituting methyl 4-bromo-2-thiophenecarboxylate for methyl 4-bromo-5-chloro-2-thiophenecarboxylate. LCMS (ES) m/z 224.0 $(M+H)^+$.

b) methyl 4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate



A solution of methyl 4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate (500 mg, 2.24 mmol) and NCS (1196 mg, 8.96 mmol) in N,N-Dimethylformamide (DMF) (10 ml) was heated at 50 °C for 2hr. The reaction mixture was diluted with 50 ml of EtOAc. The organic layer was washed with H_2O (50 ml x 2) and brine (50 ml), and then concentrated to give 460 mg of a crude mixture, which was used in next step without further separation. LCMS (ES) m/z 258.0 $(M+H)^+$.

c) 4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid

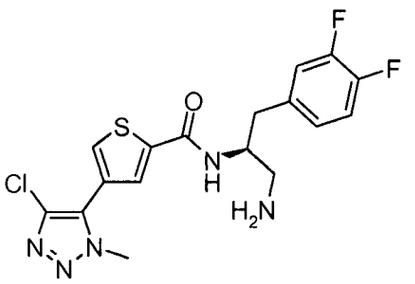


The title compound was prepared following the procedure of Example 269 b), except substituting methyl 4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylate for methyl 4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-5-chloro-2-thiophenecarboxylate. LCMS (ES) m/z 244.0$(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared following the procedure of Example 269 c-d), except substituting 4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid for 4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-5-chloro-2-thiophenecaroxylic acid and substituting 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione for 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 412.0/414.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.13 (m, 1H), 8.06 (m, 1H), 6.97 (m, 2H), 6.82 (m, 1H), 4.55 (m, 1H), 4.16 (s, 3H), 3.26 (m 2H), 3.04 (m, 2H).

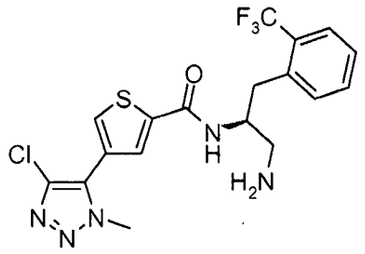
Example 274



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared following the procedure of Example 273, except substituting 2-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (82 mg, 0.15 mmol) for 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 412.0/414.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.12 (d, J=1Hz,1H), 8.05 (d, J=1Hz,1H) 7.30-7.10 (m, 3H), 4.55 (m, 1H), 4.16 (s, 3H), 3.26 (m 2H), 2.99 (m, 2H).

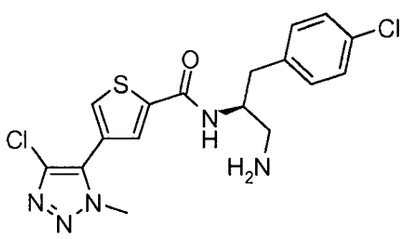
Example 275



Preparation of *N*-{(1*S*)-2-amino-1-[(2-(trifluoromethyl)phenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared following the procedure of Example 274, except substituting 2-[(2*S*)-2-amino-3-(2-(trifluoromethyl)phenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (130 mg, 0.23 mmol) for 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 444.0/446.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.13(d, J=1Hz,1H), 8.09 (d, J=1Hz,1H), 7.72 (m, 1H), 7.56 (m, 2H), 7.43 (m, 1H), 4.60 (m, 1H), 4.17 (s, 3H), 3.26-3.15(m, 4H).

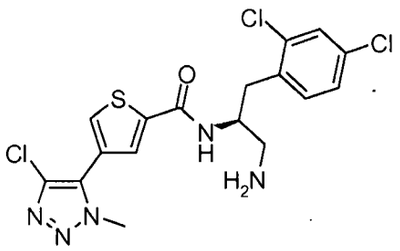
Example 276



Preparation of *N*-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared following the procedure of Example 273, except substituting 2-[(2*S*)-2-amino-3-(4-chlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (73 mg, 0.14 mmol) for 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 410.0/412.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.12(d, J=1Hz,1H), 8.03 (d,J=1Hz,1H), 7.31 (m, 4H), 4.55 (m, 1H), 4.15 (s, 3H), 3.26 (m 2H), 3.05 (m, 2H).

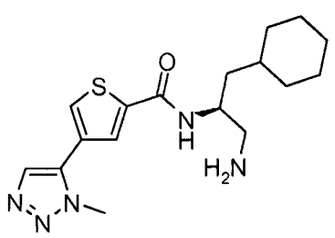
Example 277



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared following the procedure of Example 273, except substituting 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (67 mg, 0.12 mmol) for 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 444.0/448.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.12(d, J=1Hz,1H), 8.03 (d, J=1Hz, 1H), 7.49 (d, 1H), 7.38 (d, 1H), 7.25 (m, 1H), 4.60 (m, 1H), 4.16 (s, 3H), 3.30-3.09 (m, 4H).

Example 278

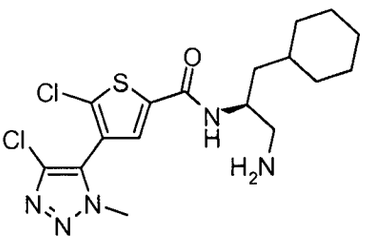


Preparation *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 263, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(cycolhexyl)propyl]carbamate (300 mg, 0.67 mmol) for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. LCMS (ES) m/z 348.2 $(M+H)^+$, 1H NMR (400

MHz, METHANOL-*d*4) δppm 8.09(d, J=1Hz,1H), 8.03 (d, J=1Hz, 1H), 7.91 (s, 1H), 4.48 (m, 1H), 4.22 (s, 3H), 3.20 (m 1H), 3.05 (m, 1H), 2.00-0.95 (m, 13H).

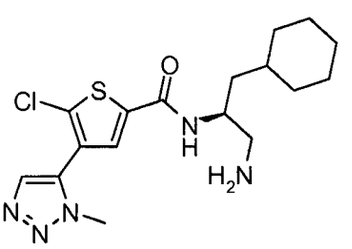
Example 279



Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-cycolhexylpropyl]carbamate (50 mg, 0.11 mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 416.0/418.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.74(s, 1H), 4.48 (m, 1H), 4.04 (s, 3H), 3.40-2.95 (m 2H), 1.90-0.95 (m, 13H).

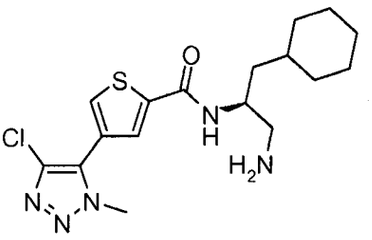
Example 280



Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 269, except substituting 2-[(2*S*)-2-amino-3-cyclohexylpropyl]-1*H*-isoindole-1,3(2*H*)-dione for 2-{(2*S*)-2-amino-3-[3-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 382.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.93 (s, 1H), 7.81 (m, 1H), 4.43 (m, 1H), 4.10 (s, 3H), 3.17 (m 1H), 3.05 (m, 1H), 2.00-0.90 (m, 13H).

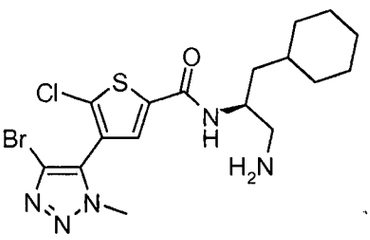
Example 281



Preparation of *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as an off white solid according to the procedure of 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-cycolhexylpropyl]carbamate (100mg, 0.22mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate, and the amount of NCS was reduced to 1eq. LCMS (ES) m/z 382.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.15(d, J=1Hz, 1H), 8.08 (d, J=1Hz,1H), 4.45 (m, 1H), 4.16 (s, 3H), 3.14 (m 1H), 3.05 (m, 1H), 2.00-0.90 (m, 13H).

Example 282

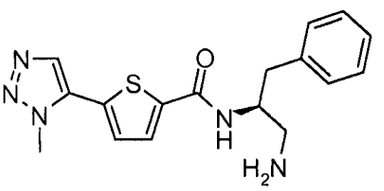


473

Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-bromo-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [(2*S*)-2-({[5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-cyclohexylpropyl]carbamate (140mg, 0.29 mmol, prepared in Example 280) and NBS (103 mg, 0.58 mmol) in 2 mL of DMF was heated at 100 °C for 2 hours. The reaction mixture was purified by reverse phase HPLC (5-65% acetonitrile in H_2O with 1% TFA) to give the title compound 14.1mg (8%) as a white solid. LCMS (ES) m/z 462.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.75 (s, 1H), 4.43 (m, 1H), 4.05 (s, 3H), 3.17 (m 1H), 3.05 (m, 1H), 2.00-0.90 (m, 13H).

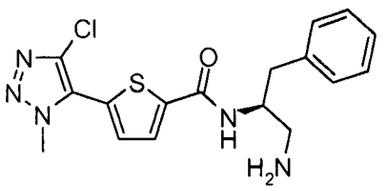
Example 283



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 260, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(5-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl]carbamate (270 mg, 0.62 mmol) for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LCMS (ES) m/z 342.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.96 (s, 1H), 7.75 (d, J=3.6Hz, 1H), 7.47 (d, J=3.6Hz, 1H), 7.31-7.22 (m, 5H), 4.55 (m, 1H), 4.21 (s, 3H), 3.20(m, 2H) 2.99 (m, 2H).

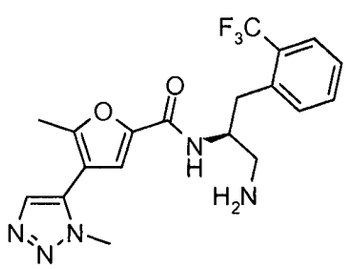
Example 284



Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[5-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate (68 mg, 0.15 mmol) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 376.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.82 (m, 1H), 7.55 (d, J=3.6Hz, 1H), 7.47 (d, J=3.6Hz, 1H), 7.32-7.23 (m, 5H), 4.55 (m, 1H),4.19 (s, 3H), 3.20(m, 2H), 3.02 (m, 2H).

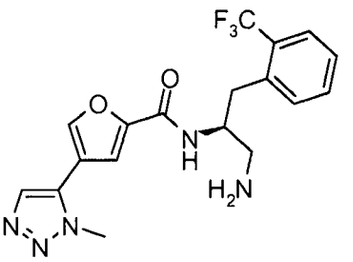
Example 285



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 269, except substituting methyl 4-bromo-5-methyl-2-furanocarboxylate (ref. Bach, T.; Kruger, L. *Synlett* **1998**, 1185-1186) for methyl 4-bromo-5-chloro-2-thiophenecarboxylate. LCMS (ES) m/z 408.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.09 (s, 1H), 7.71 (m, 1H), 7.55 (m, 2H), 7.43 (m, 2H), 4.68 (m, 1H), 4.13 (s, 3H), 3.25-3.15 (m, 4H), 2.48 (s, 3H).

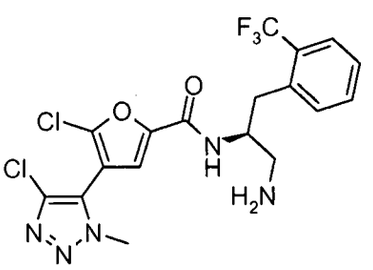
Example 286



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 260, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-furanyl)carbonyl]amino}-3-(2-(trifluoromethyl)phenyl)propyl]carbamate (200 mg, 0.4 mmol) for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LCMS (ES) m/z 394.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.23 (s, 1H), 7.93 (s, 1H), 7.71 (d, 1H), 7.54 (m, 2H), 7.43 (m, 2H), 4.75 (m, 1H), 4.18 (s, 3H), 3.30-3.10(m, 4H).

Example 287

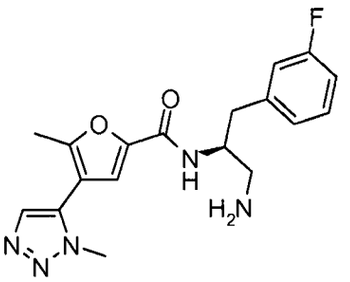


Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to the procedure of Example 261, except substituting 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furanyl]carbonyl}amino)-3-(2-(trifluoromethyl)phenyl)propyl]carbamate (90 mg, 0.18 mmol) for 1,1-dimethylethyl

[(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate. LCMS (ES) m/z 462.0/464.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.73 (m, 1H), 7.56 (m, 2H), 7.45 (m, 1H), 7.40 (s, 1H), 4.75 (m, 1H), 4.05 (s, 3H), 3.30-3.10 (m, 4H).

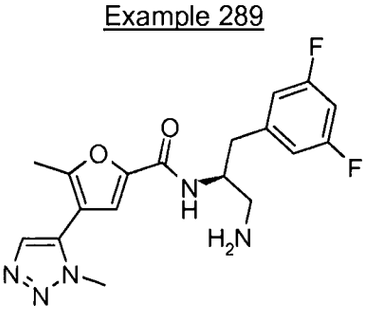
Example 288



Preparation of *N*-((1*S*)-2-amino-1-{[3-fluorophenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 269, except substituting methyl 4-bromo-5-methyl-2-furanocarboxylate for methyl 4-bromo-5-chloro-2-thiophenecarboxylate and 2-{(2*S*)-2-amino-3-[3-fluorophenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 358.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.47 (s, 1H), 7.44 (s, 1H), 7.35 (m, 1H), 7.15 (m, 2H), 6.96 (m, 1H), 4.65 (m, 1H), 4.22 (s, 3H), 3.25 (m, 2H), 3.04(m, 2H), 2.49 (s, 3H).

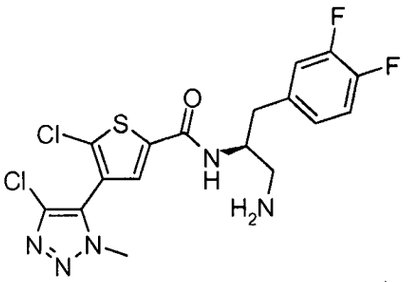
Example 289



Preparation of *N*-((1*S*)-2-amino-1-{[3,5-difluorophenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

The title compound was prepared as an off-white solid according to the procedure of Example 269, except substituting methyl 4-bromo-5-methyl-2-furanocarboxylate for methyl 4-bromo-5-chloro-2-thiophenecarboxylate and 2-{(2*S*)-2-amino-3-[3,5-difluorophenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LCMS (ES) m/z 376.2 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 8.30 (s, 1H), 7.43 (s, 1H), 6.95 (m, 2H), 6.82 (m, 1H), 4.53 (m, 1H), 4.18 (s, 3H), 3.25 (m, 2H), 3.07(m, 2H), 2.48 (s, 3H).

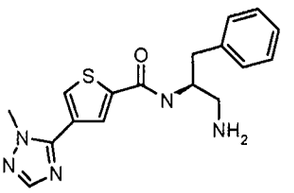
Example 290



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

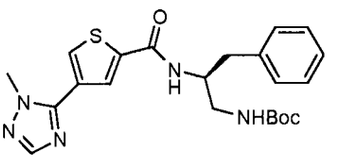
The title compound was prepared as a white solid according to the procedure of Example 261, except substituting *N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide (prepared according to Example 263) for 1,1-dimethylethyl [(2*S*)-2-({[4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate and following Example 269 for deprotection. LCMS (ES) m/z 446.0/448.0 $(M+H)^+$, 1H NMR (400 MHz, METHANOL-*d*4) δppm 7.88 (s, 1H), 7.20-7.15 (m, 3H), 4.53 (m, 1H), 4.05 (s, 3H), 3.23 (m, 2H), 3.00 (m, 2H).

Example 291



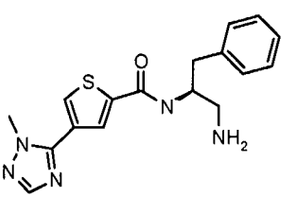
Preparation of *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [(2S)-2-({[4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate



A suspension of 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (prepared according to preparation 22 except substituting 2-[(2S)-2-amino-3-phenylpropyl]-1H-isoindole-1,3(2H)-dione for 2-[(2S)-2-amino-3-(2,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione) (200 mg, 0.455 mmol), 5,5,5',5'-tetramethyl-2,2'-bi-1,3,2-dioxaborinane (123 mg, 0.546 mmol), potassium acetate (134 mg, 1.366 mmol), and $PdCl_2(dppf)_2$ (16.7 mg, 0.023 mmol) in dry THF (3 ml) was charged into a sealed tube and heated to 80 °C for one hour. 5-Iodo-1-methyl-1H-1,2,4-triazole (114 mg, 0.546 mmol), 2M sodium carbonate (0.34 ml, 0.683 mmol) and $Pd(Ph_3P)_4$ (26.3 mg, 0.023 mmol) were then added. The mixture was heated at 85 °C for 2 hours. The solvent was removed and the residue was purified by biotage (70% H/E) to give the title product (120 mg, 60%)

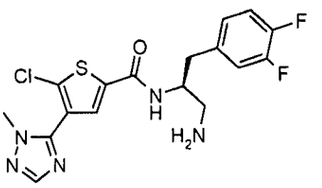
b) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide



TFA (1 ml) was added to a solution of 1,1-dimethylethyl [(2S)-2-({[4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)-3-phenylpropyl]carbamate

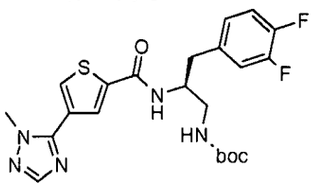
(100mg, 0.226 mmol) in DCM (5 ml). The reaction was stirred at RT for 30 min. The solvent was removed and the residue was purified by reverse phase HPLC (10% org ~ 60% org) to give the title compound as a white solid (90 mg, 87%). LC-MS (ES) m/z 342.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.23 (s, 1H), 8.03 (m, 2H), 7.22-7.31 (m, 5H), 4.60 (m, 1H), 4.08 (s, 3H), 3.10-3.20 (m, 2H), 3.00 (m, 2H).

Example 292



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl [(2*S*)-3-(3,4-difluorophenyl)-2-({[4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)propyl]carbamate



This intermediate was prepared according to the procedure of Example 291 a) except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LC-MS (ES) m/z = 478.2 $(M+H)^+$

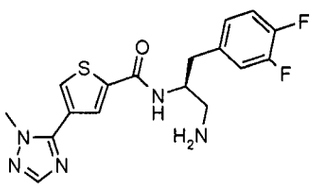
b) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

A solution of 1,1-dimethylethyl [(2*S*)-3-(3,4-difluorophenyl)-2-({[4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thienyl]carbonyl}amino)propyl]carbamate (279 mg, 0.497 mmol) and NCS (133 mg, 0.993 mmol) in N,N-Dimethylformamide (DMF) (3 ml) was heated at 110 °C for 1 hr. The crude reaction mixture was concentrated and the residue was purified by flash column chromatography on silica gel (DCM:MeOH:NH_4OH 9:1:1) to give the product as a free base, which was treated

480

with 0.13 mL of 2N HCl aq. (2 eq.) to give 75 mg of HCl salt as an off-white solid. LC-MS (ES) m/z = 412 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 8.80 (s, 1H), 8.18 (s, 1H), 7.3-7.1 (m, 3H), 4.54 (m, 1H), 4.11 (s, 3H), 3.26 (d, J = 7 Hz, 2H), 3.03 (d, J = 8 Hz, 2H).

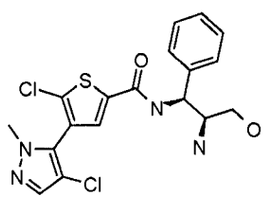
Example 293



Preparation of *N*-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared an off-white solid according to the procedure of Example 291 except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final product was purified by flash column chromatography on silica gel (DCM:MeOH:NH_4OH 9:1:1) to give a free base, which was treated with 2N HCl aq. solution to give the HCl salt. LC-MS (ES) m/z = 378 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 8.78 (s, 1H), 8.50 (d, J = 2Hz, 1H), 8.36 (d, J = 2Hz, 1H), 7.3-7.1 (m, 3H), 4.57 (m, 1H), 4.23 (s, 3H), 3.27 (d, J = 8 Hz, 2H), 3.04 (d, J = 8 Hz, 2H).

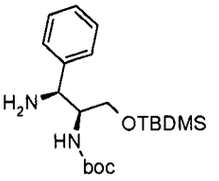
Example 294



Preparation of *N*-[(1*S*,2*S*)-2-amino-3-hydroxy-1-phenylpropyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

481

a) 1,1-dimethylethyl [(1*S*,2*S*)-2-amino-1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-phenylethyl]carbamate

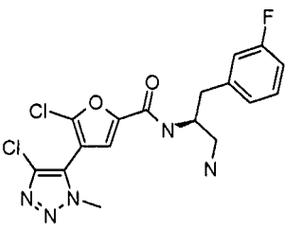


The title compound was prepared according to Preparation 1 except substituting 1,1-dimethylethyl [(1*R*,2*R*)-1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-hydroxy-2-phenylethyl]carbamate (ref. Veeresa, G.; Datta, Apurba. *Stereoselective synthesis of chloramphenicol from D-serine.* Tetrahedron Letters (**1998**), 39(46), 8503-8504.) for 1,1-dimethylethyl (2-hydroxy-2-phenylethyl)carbamate.

b) *N*-[(1*S*,2*S*)-2-amino-3-hydroxy-1-phenylpropyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

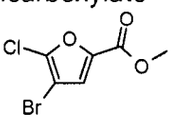
This intermediate was prepared according to the procedures of Example 261, except substituting 1,1-dimethylethyl [(1*S*,2*S*)-2-amino-1-({[(1,1-dimethylethyl)(dimethyl)silyl]oxy}methyl)-2-phenylethyl]carbamate for 1,1-dimethylethyl (2-amino-2-phenylethyl)carbamate. LC-MS (ES) m/z = 425.0/427.0 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.86 (s, 1H), 7.59 (s, 1H), 7.56-7.38 (m, 5H), 5.50 (m, 1H), 3.91-3.84 (m, 3H).

Example 295



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

a) Methyl 4-bromo-5-chloro-2-furancarboxylate



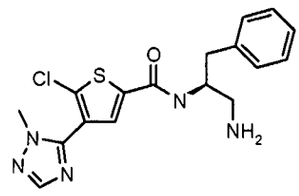
481

Isopropylmagnesium chloride (1.20 ml, 2.40 mmol) was added dropwise to a solution of methyl 4,5-dibromo-2-furancarboxylate (568 mg, 2.0 mmol) in Tetrahydrofuran (THF) (16 ml) at 0 °C. The resulting mixture was stirred at this temperature for 30 min and then cooled to -78 °C. A solution of hexylchloroethane (568 mg, 2.401 mmol) in THF (1 mL) was added dropwise, and the resulting mixture was stirred at this temperature for 1 hr. The reaction was quenched with addition of NH_4Cl (sat. aq) and the resulting mixture was stirred at rt overnight. Ether and water were added and the aqueous layer was discarded. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated to give 0.34 g of the product containing its isopropyl ester.

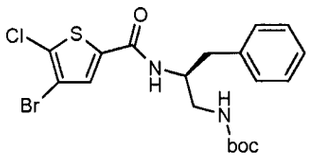
b) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide

The title compound was prepared according to the procedure of Example 273, except substituting methyl 4-bromo-5-chloro-2-furancarboxylate for methyl 4-bromo-2-thiophenecarboxylate, and substituting 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. The final product was purified by RP-HPLC and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z = 412.0/414.0 $(M+H)^+$, ^1H NMR (CD_3OD, 400 MHz) δ 7.44 (s, 1H), 7.33 (m, 1H), 7.14-7.07 (m, 2H), 6.98 (m, 1H), 4.55 (m, 1H), 4.05 (s, 3H), 3.25-2.98 (m, 4H).

Example 296



Preparation of N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide



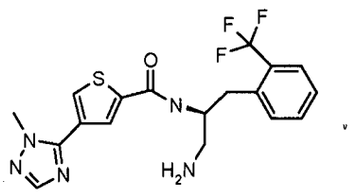
a) 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate

A solution of 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate (prepared according to Preparation 22), except substituting 2-[(2S)-2-amino-3-phenylpropyl]-1H-isoindole-1,3(2H)-dione for 2-[(2S)-2-amino-3-(2,4-dichlorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (200 mg, 0.455 mmol) and NCS (61 mg, 0.455 mmol) in DMF (3 ml) was heated at 50 °C in a sealed tube for 2 hours. The solvent was removed and the residue was purified by biotage (30% Hex/EtOAc) to give the title product (140 mg, 65%).

b) *N*-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according the procedure of Example 291, except substituting 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-5-chloro-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LC-MS (ES) m/z 376.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.12 (s, 1H), 7.74 (s, 1H), 7.31-7.35 (m, 5H), 4.58 (m, 1H), 3.94 (s, 3H), 3.35 (m, 2H), 3.05 (m, 2H).

Example 297

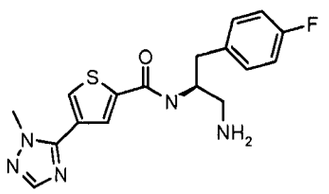


Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 291, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-

phenylpropyl)carbamate; LC-MS (ES) m/z 410.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.33 (m, 2H), 7.73 (m, 1H), 7.41-7.56 (m, 4H), 4.70 (m, 1H), 4.13 (s, 3H), 3.36 (m, 2H), 3.18 (m, 2H).

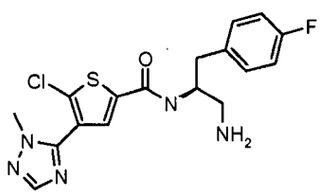
Example 298



Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 291, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-fluorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LC-MS (ES) m/z 360.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.24 (s, 1H), 8.06 (m, 2H), 7.29-7.34 (m, 2H), 7.01-7.05 (m, 2H), 4.66 (m, 1H), 4.08 (s, 3H), 3.23 (m, 2H), 3.15 (m, 2H).

Example 299

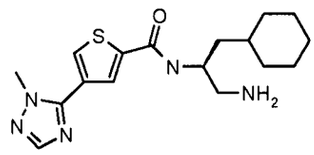


Preparation of *N*-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 292, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-fluorophenyl)propyl]carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-

difluorophenyl)propyl]carbamate. The final compound was purified by RP-HPLC to give the title compound as a white solid. LC-MS (ES) m/z 394.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.10 (s, 1H), 7.70 (s, 1H), 7.28-7.31 (m, 2H), 7.01-7.06 (m, 2H), 4.56 (m, 1H), 3.92 (s, 3H), 3.21 (m, 2H), 2.96 (m, 2H).

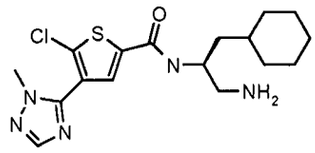
Example 300



Preparation of *N*-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 291, except substituting 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-cyclohexylpropyl)carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. LC-MS (ES) m/z 348.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.27 (m, 1H), 8.13 (s, 1H), 8.02 (s, 1H), 4.56 (m, 1H), 4.11 (s, 3H), 3.16 (m, 1H), 3.02 (m, 1H), 1.17-1.95 (m, 13H)

Example 301

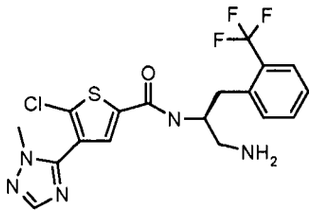


Preparation of N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 292, except substituting 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-cyclohexylpropyl)carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. The final compound was purified by RP-HPLC to

give the title compound as a white solid. LC-MS (ES) m/z 382.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.10 (s, 1H), 7.82 (s, br, 1H), 4.42 (m, 1H), 3.94 (s, 3H), 3.16-3.30 (m, 1H), 2.98-3.10 (m, 1H), 1.06-1.96 (m, 13H)

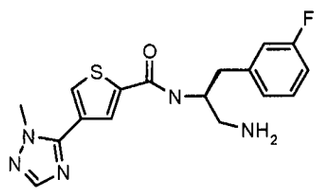
Example 302



Preparation of N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 292, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate; The final compound was purified by RP-HPLC to give the title compound as a white solid. LC-MS (ES) m/z 444.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.20 (s, br, 1H), 7.86 (s, br, 1H), 7.71 (m, 1H), 7.42-7.56 (m, 3H), 4.63 (m, 1H), 3.96 (s, 3H), 3.09-3.27 (m, 4H).

Example 303

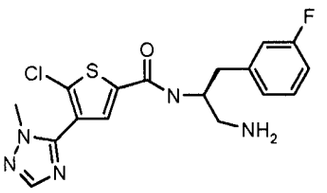


Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 291, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3-fluorophenyl)propyl]carbamate for 1,1-dimethylethyl

((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate; LC-MS (ES) m/z 360.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.24 (s, 1H), 8.02 (m, 2H), 7.30 (m, 1H) 7.06-7.13 (m, 2H), 6.96 (m, 1H), 4.63 (m, 1H), 4.08 (s, 3H), 3.09-3.27 (m, 4H).

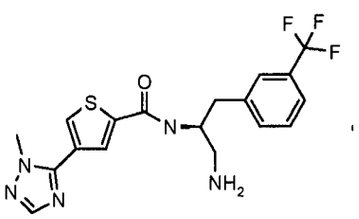
Example 304



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 292, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3-fluorophenyl)propyl]carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate; The final compound was purified by RP-HPLC to give the title compound as a white solid. LC-MS (ES) m/z 394.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.10 (s, 1H), 7.70 (s, 1H), 7.31 (m, 1H), 6.97-7.11 (m, 3H), 4.52 (m, 1H), 3.92 (s, 3H), 2.96-3.26 (m, 4H)

Example 305

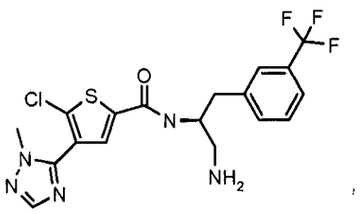


Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 291, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-2-

thienyl)carbonyl]amino}-3-[3-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate; The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 410.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.81 (s, 1H), 8.51 (d, J=1Hz, 1H), 8.39 (d, J=1Hz, 1H), 7.64 (m, 2H), 7.50 (m, 2H), 4.66 (m, 1H), 4.23 (s, 3H), 3.30 (m, 2H), 3.15 (m, 2H).

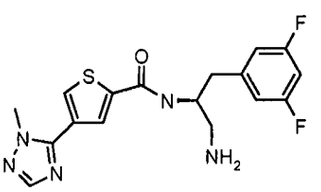
Example 306



Preparation of *N*-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 292, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-[3-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 440.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.53 (s, 1H), 8.02 (s, 1H), 7.50-7.64 (m, 4H), 4.56 (m, 1H), 4.03 (s, 3H), 3.10-3.27 (m, 4H).

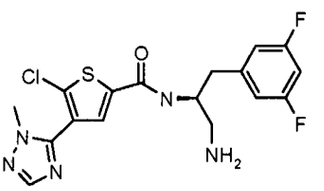
Example 307



Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 291, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,5-difluorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate; The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 378.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.68 (s, 1H), 8.47 (d, J=1Hz, 1H), 8.35 (d, J=1Hz, 1H), 6.96 (m, 2H), 6.80 (m,1H), 4.60 (m, 1H), 4.21 (s, 3H), 3.28 (m, 2H), 3.08 (m, 2H).

Example 308

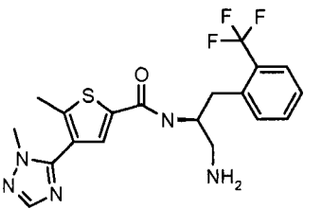


Preparation of N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 292, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,5-difluorophenyl)propyl]carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate; The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 412.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.44 (s, 1H), 7.98 (s, 1H), 6.96 (m, 2H), 6.82 (m, 1H), 4.66 (m, 1H), 4.01 (s, 3H), 3.20-3.25 (m, 2H), 3.02-3.05 (m, 2H).

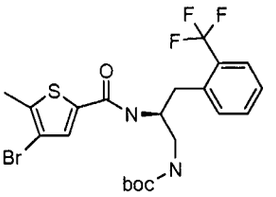
Example 309

490



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

a) 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-5-methyl-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate

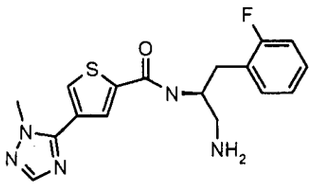


This intermediate was prepared according to Preparation 22, except substituting 4-bromo-5-methyl-2-thiophenecarboxylic acid (Bioorganic & Medicinal Chemistry Letters (2002), 12(3), 491-495) for 4-bromo-2-thiophenecarboxylic acid, and substituting 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione for 2-[(2*S*)-2-amino-3-(2,4-dichlorophenyl)propyl]-1*H*-isoindole-1,3(2*H*)-dione.

b) *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 291, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-5-methyl-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate: The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 424.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.68 (s, 1H), 8.04 (s, 1H), 7.70 (m, 1H), 7.58 (m, 1H), 7.52 (m, 1H), 7.43 (m, 1H), 4.65 (m, 1H), 4.05 (s, 3H), 3.16-3.28 (m, 4H), 2.59 (s, 3H)

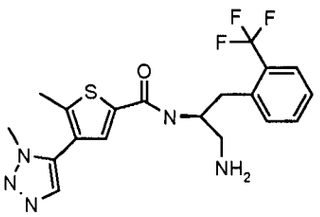
Example 310



Preparation of *N*-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 291, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(2-fluorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate; LC-MS (ES) m/z 360.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.60 (s, 1H), 8.43 (d, J=1Hz, 1H), 8.24 (d, J=1Hz, 1H), 7.37 (m, 1H), 7.27 (m, 1H), 7.08 (m, 2H), 4.66 (m, 1H), 4.19 (s, 3H), 3.27 (m, 2H), 3.10 (s, 2H)

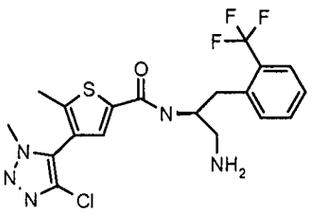
Example 311



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 260, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-5-methyl-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 360.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.31 (s, 1H), 7.94 (s, 1H), 7.70 (m, 1H), 7.56 (m, 2H), 7.43 (m, 1H), 4.65 (m, 1H), 4.19 (s, 3H), 3.15-3.28 (m, 4H), 2.50 (s, 3H).

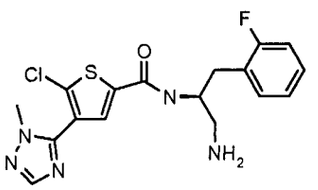
Example 312



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 261, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-5-methyl-2-thienyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl ((2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 458.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.70 (m, 2H), 7.55 (m, 2H), 7.44 (m, 1H), 4.67 (m, 1H), 3.99 (s, 3H), 3.12-3.21 (m, 4H), 2.42 (s, 3H).

Example 313



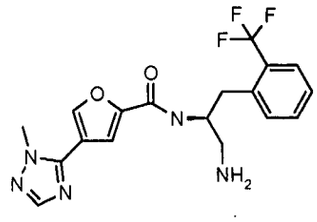
Preparation of *N*-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 292, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-fluorophenyl)propyl]carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 394.2

493

$(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.49 (s, 1H), 7.95 (s, 1H), 7.27-7.36 (m, 2H), 7.06-7.13 (m, 2H), 4.61 (m, 1H), 4.03 (s, 3H), 3.02-3.25 (m, 4H).

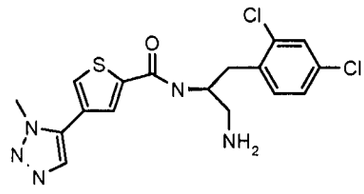
Example 314



Preparation of *N*-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-furancarboxamide

The title compound was prepared as a white solid according to Example 291, except substituting 1,1-dimethylethyl {(2*S*)-2-{[(4-bromo-2-furanyl)carbonyl]amino}-3-[2-(trifluoromethyl)phenyl]propyl}carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 394.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.50 (s, 1H), 8.43 (s, 1H), 7.71 (m, 1H), 7.61 (s, 1H), 7.54 (m, 2H), 7.42 (m, 1H), 4.66 (m, 1H), 4.14 (s, 3H), 3.25 (m, 2H), 3.14 (m, 2H).

Example 315

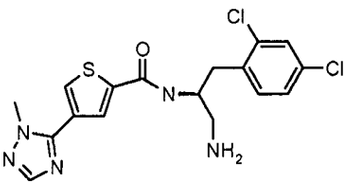


Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 260, except substituting 1,1-dimethylethyl [(2S)-2-{[(4-bromo-2-

thienyl)carbonyl]amino}-3-(2,4-dichlorophenyl)propyl]carbamate (from Preparation 22) for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 410.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.23 (s, 1H), 8.14 (m, 2H), 7.47 (d, J=1Hz, 1H), 7.41 (d, J=1Hz, 1H), 7.25 (m, 1H), 4.68 (m, 1H), 4.30 (s, 3H), 3.11-3.28 (m, 4H).

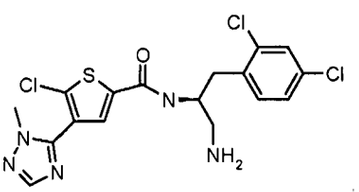
Example 316



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 291, except substituting 1,1-dimethylethyl [(2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(2,4-dichlorophenyl)propyl]carbamate (from Preparation 22) for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 410.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.71 (s, 1H), 8.47 (d, J=1Hz, 1H), 8.34 (d, J=1Hz, 1H), 7.45 (m, 2H), 7.23 (m, 1H), 4.71 (m, 1H), 4.23 (s, 3H), 3.14-3.22 (m, 4H)

Example 317

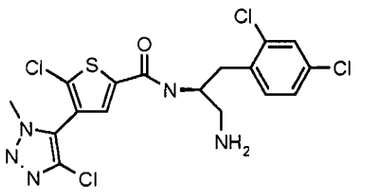


495

Preparation of N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 292, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(2,4-dichlorophenyl)propyl]carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 446.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.65 (s, 1H), 8.11 (s, 1H), 7.44 (m, 2H), 7.25 (m, 1H), 4.68 (m, 1H), 4.08 (s, 3H), 3.10-3.23 (m, 4H).

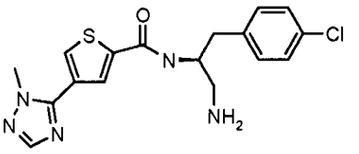
Example 318



Preparation of *N*-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 261, except substituting 1,1-dimethylethyl [(2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(2,4-dichlorophenyl)propyl]carbamate (from Preparation 21) for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 480.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.80 (m, 1H), 7.48 (m, 1H), 7.39 (m, 1H), 7.27 (m, 1H), 4.66 (m, 1H), 4.05 (s, 3H), 3.08-3.14 (m, 4H)

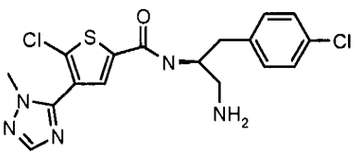
Example 319



Preparation of *N*-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 291, except substituting 1,1-dimethylethyl [(2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-chlorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 376.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.68 (s, 1H), 8.46 (d, J=1Hz, 1H), 8.29 (d, J=1Hz, 1H), 7.27-7.34 (m, 4H), 4.57 (m, 1H), 4.21 (s, 3H), 3.25 (m, 2H), 3.04 (m, 2H)

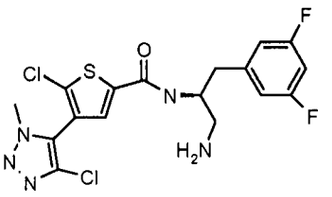
Example 320



Preparation of *N*-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 292, except substituting 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-chlorophenyl)propyl]carbamate for 1,1-dimethylethyl [(2*S*)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,4-difluorophenyl)propyl]carbamate. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 410.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.47 (s, 1H), 7.97 (s, 1H), 7.30 (m, 4H), 4.60 (m, 1H), 4.03 (s, 3H), 3.22 (m, 2H), 3.00 (m, 2H).

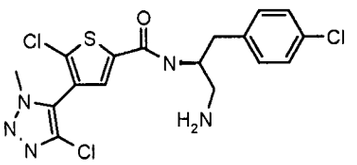
Example 321



Preparation of N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to Example 261, except substituting 1,1-dimethylethyl [(2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(3,5-difluorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate; The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 446.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.80 (s, 1H), 6.95 (m, 2H), 6.84 (m, 1H), 4.62 (m, 1H), 4.04 (s, 3H), 3.20 (m, 2H), 3.01 (m, 2H).

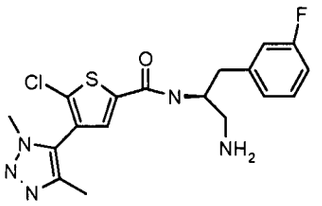
Example 322



Preparation of *N*-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

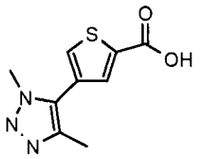
The title compound was prepared as a white solid according to Example 261, except substituting 1,1-dimethylethyl [(2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-(4-chlorophenyl)propyl]carbamate for 1,1-dimethylethyl ((2S)-2-{[(4-bromo-2-thienyl)carbonyl]amino}-3-phenylpropyl)carbamate; The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 444.0 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.73 (s, 1H), 7.30 (m, 4H), 4.66 (m, 1H), 4.04 (s, 3H), 3.18 (m, 2H), 2.99 (m, 2H).

Example 323



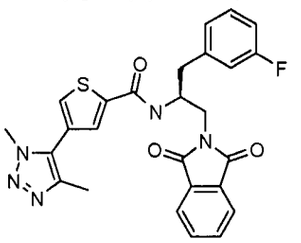
Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

a) 4-(1,4-dimethyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid



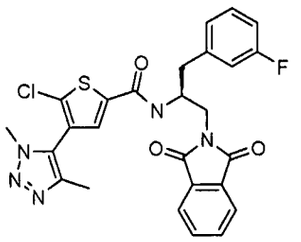
This intermediate was prepared according to the procedures of Example 269 a) and b) except substituting 1,4-dimethyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole (from Preparation 21) for 1-methyl-5-(tributylstannanyl)-1*H*-1,2,3-triazole and substituting methyl 4-bromo-2-thiophenecarboxylate for methyl 4-bromo-5-chloro-2-thiophenecarboxylate. LC-MS (ES) m/z 224.2 $(M+H)^+$.

b) 4-(1,4-Dimethyl-1H-1,2,3-triazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide



This intermediate was prepared according to the procedure of Example 269 c) except substituting 4-(1,4-dimethyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid for 5-chloro-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxylic acid, and substituting 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione for 2-{(2*S*)-2-amino-3-[2-(trifluoromethyl)phenyl]propyl}-1*H*-isoindole-1,3(2*H*)-dione. LC-MS (ES) m/z 504.2 $(M+H)^+$.

c) 5-chloro-4-(1,4-dimethyl-1*H*-1,2,3-triazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide

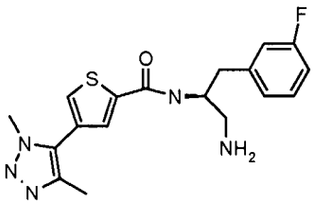


A solution of 4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-N-{(1S)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide (254 mg, 0.454 mmol), and NCS (60.6 mg, 0.454 mmol) in N,N-Dimethylformamide (DMF) (5 mL) to was heated at 40 °C overnight. The reation mixture was taken into EtOAc, which was washed with H_2O 3X and brine, dried (Na_2SO_4) and concentrated. The residue was purified on a 25g Biotage column, which was eluted with 50-100% EtOAc /hexane to give 76 mg (28%) of product as a white foamy solid and 63 mg of recovered starting material. LC-MS (ES) m/z 538.0 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 269 d), except substituting 5-chloro-4-(1,4-dimethyl-1*H*-1,2,3-triazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide for 5-chloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide. The final compound was purified by RP-HPLC, and converted to HCl salt with 2N HCl aqueous solution. LC-MS (ES) m/z 408.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.88 (m, 1H), 7.30 (m, 1H), 7.10 (m, 2H), 6.96 (m, 1H), 4.65 (m, 1H), 4.10 (s, 3H), 3.21 (m, 2H), 3.03 (m, 2H), 2.06 (s, 3H).

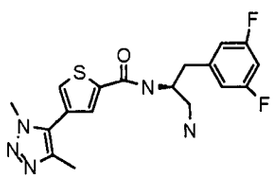
Example 324



Preparation of *N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedures of Example 323 a), b) and d), except substituting 4-(1,4-dimethyl-1*H*-1,2,3-triazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide for 5-chloro-4-(1,4-dimethyl-1*H*-1,2,3-triazol-5-yl)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)-1-[(3-fluorophenyl)methyl]ethyl}-2-thiophenecarboxamide. LC-MS (ES) m/z 374.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.09 (d, J=1Hz, 1H), 8.06 (d, J=1Hz, 1H), 7.31 (m, 1H), 7.16 (m, 1H), 6.96 (m, 1H), 4.56 (m, 1H), 4.20 (s, 3H), 3.23 (m, 2H), 3.05 (m, 2H), 2.47 (s, 3H).

Example 325

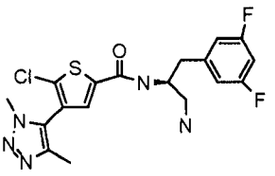


Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedures of Example 323 a), b) and d), except substituting 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione. LC-MS (ES) m/z 392.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 8.13 (m, 2H), 6.99 (m, 2H), 6.79 (m, 1H), 4.59 (m, 1H), 4.22 (s, 3H), 3.26 (m, 2H), 3.06 (m, 2H), 2.49 (s, 3H).

101

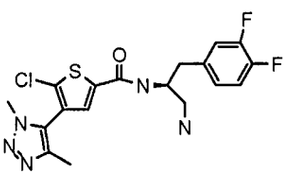
Example 326



Preparation of *N*-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

The title compound was prepared as a white solid according to the procedure of Example 323, except substituting 2-[(2*S*)-2-amino-3-(3,5-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione. LC-MS (ES) m/z 426.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.88 (s, 1H), 6.96 (m, 2H), 6.82 (m, 1H), 4.62 (m, 1H), 4.07 (s, 3H), 3.22 (m, 2H), 3.05 (m, 2H), 2.34 (s, 3H).

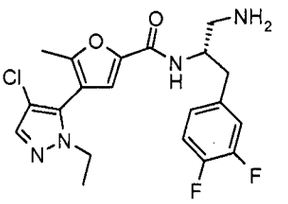
Example 327



Preparation of *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide

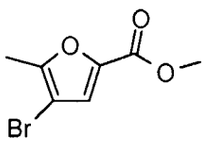
The title compound was prepared as a white solid according to the procedure of Example 323, except substituting substituting 2-[(2*S*)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione for 2-[(2*S*)-2-amino-3-(3-fluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione. LC-MS (ES) m/z 426.2 $(M+H)^+$, ^1H NMR (d_4-MeOH, 400 MHz) δ 7.87 (s, 1H), 7.12-7.26 (m, 3H), 4.62 (m, 1H), 4.08 (s, 3H), 3.21 (m, 2H), 3.00 (m, 2H), 2.36 (s, 3H).

Example 328



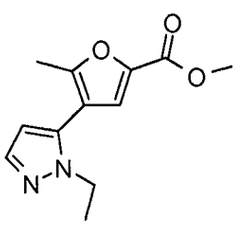
N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide

a) methyl 4-bromo-5-methyl-2-furancarboxylate



To a solution of methyl 4,5-dibromo-2-furancarboxylate (4.5 g, 15.85 mmol) and BIS(TRIPHENYLPHOSPHINE)PALLADIUM(II) CHLORIDE (0.38 g, 0.541 mmol) in THF (100 mL) at RT was added chloro(methyl)zinc (15 mL, 30 mmol) dropwise. After stirring for 10h, the reaction was quenched with NH_4Cl (sat'd) (50 mL). The mixture was extracted with EtOAc (50 mL x 3), and the collected organic layers were dried over $MgSO_4$. Solvent was removed under vaccum and the resulting residue was purified via column chromatography (silica, EtOAc/Hex 10-20%) to give the title compound (2.5 g, 72%) as a white solid: LC-MS (ES) m/z 220 $(M+H)^+$.

b) methyl 4-(1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxylate

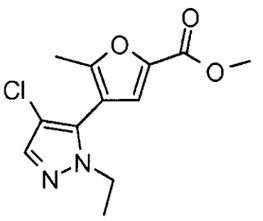


To a 100 mL sealed flask was added 1-ethyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (2.2 g, 9.91 mmol), potassium carbonate (2.84 g, 20.54 mmol), methyl 4-bromo-5-methyl-2-furancarboxylate(1.5 g, 6.85 mmol) and BIS(TRI-T-BUTYLPHOSPHINE)PALLADIUM(0) (0.175 g, 0.34 mmol) in 1,2-dimethoxyethane (6 mL) and H_2O (1 mL). After stirring for 2h at 72 °C, the reaction

103

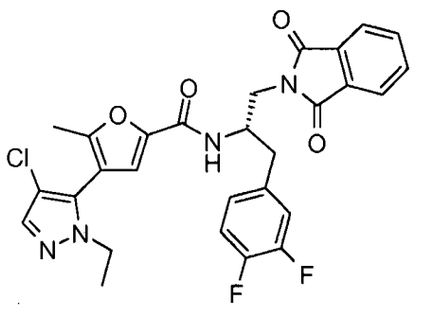
solution was diluted with DCM (50 mL) and washed with H_2O. The organic layer was dried Na_2SO_4, filtered and concentrated. The residue was purified on silica gel [EtOAC/hexanes, 10-30%] to give the product [1.1 g, 68.6%] as an off white solid: LC-MS (ES) m/z 235 $(M+H)^+$.

c) methyl 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxylate



A mixture of methyl 4-(1-ethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (950 mg, 4.06 mmol) and NCS (650 mg, 4.87 mmol) in THF (10 mL) was heated at 70 ^oC in a sealed tube. After 2h, the reaction mixture was concentrated and purified via column chromatography (silica, 10-20% EtOAc/Hexane) affording the title compound (970 mg, 89%) as a white solid: LC-MS (ES) m/z 269 $(M+H)^+$.

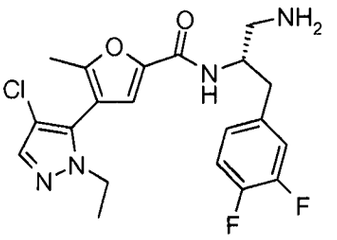
d) 4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-*N*-{(1*S*)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]ethyl}-5-methyl-2-furancarboxamide



To a solution of methyl 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxylate (500 mg, 1.86 mmol) in THF/H_2O (5mL/1 mL) was added KOH (500 mg, 8.91 mmol). The reaction mixture was heated to 50° C for 4 h. The mixture was concentrated, diluted with H_2O (2 mL) and the pH was adjusted to 3. The mixture was extracted with DCM (10 mL x 3). The collected organic layers were concentrated under vacuum to give a crude acid (460 mg, 97%), which was used directly without of further purification: LC-MS (ES) m/z 255 $(M+H)^+$.

To the above acid (221 mg, 0.869 mmol) in DCM (5 mL) at 25 °C was added PyBrOP(480 mg, 1.03 mmol) in one portion, followed by addition of DIPEA (1.0 mL, 5.73 mmol). After 10 min, 2-[(2S)-2-amino-3-(3,4-difluorophenyl)propyl]-1H-isoindole-1,3(2H)-dione (250 mg, 0.79 mmol) was added to the reaction solution. After 1h, the reaction mixture was concentrated and purified via column chromatography (silica, 30-50 % EtOAc/Hexane) affording the title compound (401 mg, 92%) as a white solid: LC-MS (ES) m/z 553 $(M+H)^+$.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide



At rt, NH_2NH_2 (0.5 mL, 15.93 mmol) was added to 4-(4-chloro-1-ethyl-1H-pyrazol-5-yl)-N-{(1S)-2-(3,4-difluorophenyl)-1-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]ethyl}-5-methyl-2-furancarboxamide (260 mg, 0.47 mmol) in MeOH (5 mL) . After 48h, the solvent was removed under vaccum. The resulting residue was taken into DCM (20 mL), and washed with H_2O (20 mL x 3).

To the DCM solution was added HCl (36%, 10 mL, 120 mmol). After 1h, the aqueous phase was separated, and washed with DCM (30 ml x 3). Water was removed under high vacuum to give the title compound (140 mg, 69.7%) as an off-white solid: LC-MS (ES) m/z 423 $(M+H)^+$, NMR (d_4-MeOD, 400 MHz) δ ppm 7.59 (s, 1H), 7.27-7.16 (m, 3H), 7.13-7.08 (m, 1H), 4.56 (m, 1H), 4.06 (q, J = 7.3 Hz, 2H), 3.26-3.22 (m, 1H), 3.17-3.11 (m, 1H), 3.05-3.00 (m, 1H), 2.97-2.91 (m, 1H), 2.36 (s, 3H), and 1.33 (t, J = 7.3 Hz, 3H).

Example 329 - Capsule Composition

An oral dosage form for administering the present invention is produced by filing a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

Table I

INGREDIENTS	AMOUNTS
N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide (Compound of Example 1)	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 330 - Injectable Parenteral Composition

An injectable form for administering the present invention is produced by stirring 1.5% by weight of *N*-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide (Compound of Example 2) in 10% by volume propylene glycol in water.

Example 331 - Tablet Composition

The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid;, screened and compressed into a tablet.

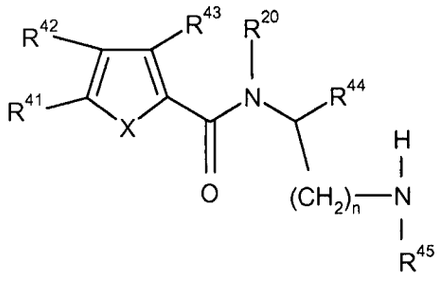
Table II

INGREDIENTS	AMOUNTS
N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide (Compound of Example 3)	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

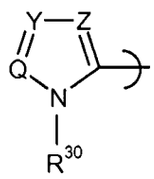
What is claimed is:

1. A compound of Formula (I):



(I)

wherein:

R^{41} and R^{42} are independently selected from: hydrogen,  , halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan, substituted fruan, thiophene and substituted thiophene,

where Q and Y are independently selected from: nitrogen and $-C(R^{70})-$, and Z is selected from: nitrogen and $-C(R^{48})-$, provided that at least one and at most 2 of Q, Y and Z are nitrogen, and R^{30} is selected from: C_{1-4}alkyl and C_{1-4}alkyl substituted with form one to three fluorine atoms,

where R^{70} is selected from: hydrogen, and halogen, and

R^{48} is selected from: hydrogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, cylcoalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl, substituted C_{1-4}alkyl, C_{1-4}alkyloxy, substituted C_{1-4}alkyloxy, furan and thiophene;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAR$ wherein the AR is unsubstituted, $-(CR^{60}R^{61})_mAR$ wherein the AR is substituted and C_{1-6}alkyl,

where m is 0 to 3 and AR is a cyclic or polycyclic aromatic or saturated or unsaturated non-aromatic ring containing from 3 to 16 carbon atoms and optionally containing from one to three heteroatoms, provided that when the ring is aromatic and the number of carbon atoms is 3 the ring contains at least two heteroatoms and when the ring is aromatic and the number of carbon atoms is 4 the ring contains at least one heteroatom, and R^{60} and R^{61} are independently selected from: hydrogen and C_{1-4}alkyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are C_{1-4}alkyl,

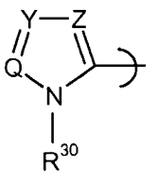
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, C_{1-4}alkyl and hydroxy;

X is selected from O, S and NR^{49},

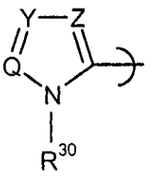
where R^{49} is selected from hydrogen and C_{1-4}alkyl; and

n is 0 to 2 and this moiety is optionally, if applicable, substituted by hydroxyC_{1-4}alkyl;

provided that one and only one of R^{41} and R^{42} is  ;

and/or a pharmaceutically acceptable salt thereof.

2. A compound of Formula (I), as defined in Claim 1, wherein:

R^{41} and R^{42} are independently selected from: hydrogen,  ,
halogen, C_{1-4}alkyl, trifluoromethyl, methoxy and furan,
where Q is nitrogen, Y is selected from: nitrogen and
$-C(R^{70})-$, and Z is selected from: nitrogen and
$-C(R^{48})-$, provided that at most one of Y and Z are nitrogen, and
R^{30} is C_{1-4}alkyl,
where R^{70} is selected from: hydrogen, and halogen, and
R^{48} is selected from: hydrogen, C_{1-4}alkyl, trifluoromethyl, phenyl, cylcopropyl, and halogen;

R^{43} is selected from: hydrogen, halogen, C_{1-4}alkyl and methoxy;

R^{44} is absent or selected from: $-(CR^{60}R^{61})_mAAR$ wherein the AAR is unsubstituted, $-(CR^{60}R^{61})_mAAR$ wherein the AAR is substituted and C_{1-6}alkyl,
where m is 0 to 3 and AAR is selected from phenyl, indole, naphthalene, pyridine and cyclohexyl, and

109

R^{60} and R^{61} are independently selected from: hydrogen and methyl, provided that when m is 3 no more than 4 of R^{60} and R^{61} when added together are methyl,

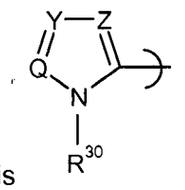
R^{45} is selected from hydrogen and C_{1-4}alkyl;

R^{20} is selected from hydrogen, methyl and hydroxy;

X is selected from O, S and NR^{49},

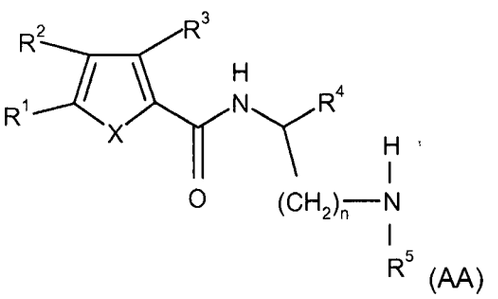
where R^{49} is selected from hydrogen and methyl; and

n is 1 to 2 and this moiety is optionally substituted by hydroxylmethyl;

provided that one and only one of R^{41} and R^{42} is  ;

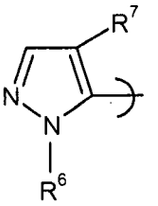
and/or pharmaceutically acceptable salts thereof.

3. A compound of Claim 1 represented by the following Formula (AA):



(AA)

wherein:

R^1 and R^2 are independently selected from: hydrogen,  , halogen, C_{1-4}alkyl, furan and thiophene,

where R^6 is C_{1-4}alkyl and R^7 is selected from hydrogen, C_{1-4}alkyl and halogen;

R^3 is selected from: hydrogen, halogen, C_{1-4}alkyl, furan and thiophene;

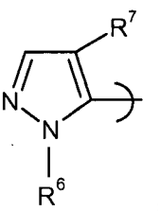
R^4 is selected from $-(CH_2)_m$aryl and $-(CH_2)_m$aryl wherein the aryl is substituted,

where m is 0 to 2;

R^5 is selected from hydrogen and C_{1-4}alkyl;

X is selected from O and S; and

n is 0 to 2;

provided that one and only one of R^1 and R^2 is  and further provided that at least one of R^1, R^2 and R^3 is hydrogen;

and/or a pharmaceutically acceptable salt thereof.

4. A compound of claim 1 selected from:

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide;

N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(3-furanyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-3-(methyloxy)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[3-amino-1-(phenylmethyl)propyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-N-[2-(methylamino)-1-phenylethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(4-bromo-1-methyl-1H-pyrazol-5-yl)-4-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-fluoro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[1-(aminomethyl)-3-phenylpropyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-3-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-*N*-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[3-(methylamino)-1-phenylpropyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

4-bromo-*N*-[2-(methylamino)-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide

N-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-1-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-1*H*-pyrrole-2-carboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-(methylamino)-1-(phenylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[1-(aminomethyl)-2-methyl-2-phenylpropyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[4-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1*H*-imidazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(1*H*-indol-3-ylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(1-naphthalenyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(1-naphthalenyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{2-amino-1-[2-(trifluoromethyl)phenyl]ethyl}-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(3-amino-1-phenylpropyl)-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3,4-dibromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-*N*-hydroxy-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3-(methyloxy)-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-fluoro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-[1-methyl-4-(1-methylethyl)-1H-pyrazol-5-yl]-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-propyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-ethyl-4-(1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1-methyl-4-propyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-4-ethyl-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,6-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-cyclopropyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(3-chloro-1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-ethyl-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(methyloxy)-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(2,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-chloro-5-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(3-pyridinylmethyl)ethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*R*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-fluorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[2-amino-1-(2-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(3-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-aminoethyl)-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(4-chlorophenyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-phenylethyl]-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-[(1*S*)-2-amino-1-methylethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[3-(trifluoromethyl)phenyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-[(1*S*)-1-(aminomethyl)-3-methylbutyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-pyrazol-5-yl)-5-(trifluoromethyl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

(*N*-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1,4-diethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-ethyl-4-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-3-methyl-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-[1-methyl-4-(trifluoromethyl)-1*H*-pyrazol-5-yl]-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-propyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(4-bromo-1-methyl-1H-1,2,3-triazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

527

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(phenylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1*H*-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1S)-2-amino-1-(cyclohexylmethyl)ethyl]-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

J28

N-{(1S)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-methyl-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(2,4-dichlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(4-chlorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,5-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-1,2,3-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(1-methyl-1H-1,2,4-triazol-5-yl)-2-thiophenecarboxamide;

N-[(1*S*,2*S*)-2-amino-3-hydroxy-1-phenylpropyl]-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-1,2,3-triazol-5-yl)-2-furancarboxamide; and

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-5-methyl-2-furancarboxamide;

and/or a pharmaceutically acceptable salt thereof.

5. A pharmaceutical composition comprising a compound according to claim 1, and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

6. A process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier or diluent and an effective amount of a compound of Formula (I) as described in claim 1 and/or a pharmaceutically acceptable salt thereof, which process comprises bringing the compound of Formula (I) and/or a pharmaceutically acceptable salt thereof into association with a pharmaceutically acceptable carrier or diluent.

7. A method of treating or lessening the severity of a disease or condition selected from: cancer and arthritis, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula I, as described in claim 1 and/or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein the mammal is a human.

9. A method of treating or lessening the severity of a disease or condition selected from: cancer and arthritis, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula (AA), as described in claim 3 and/or a pharmaceutically acceptable salt thereof.

10. The method of claim 9 wherein the mammal is a human.

11. The method according to claim 7 wherein said cancer is selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

12. The method according to claim 9 wherein: said cancer is selected from brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma and thyroid.

13. Use of a compound of Formula (I), as described in claim 1 and/or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in treating or lessening the severity of a disease or condition selected from cancer and arthritis.

14. The method of inhibiting Akt activity in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of Formula I, as described in claim 1 and/or a pharmaceutically acceptable salt thereof.

15. The method of claim 14 wherein the mammal is a human.

16. A method of treating cancer in a mammal in need thereof, which comprises: administering to such mammal a therapeutically effective amount of

a) a compound of Formula (I), as described in claim 1 and/or a pharmaceutically acceptable salt thereof; and

b) at least one anti-neoplastic agent.

17. The method claim 16, wherein the at least one anti-neoplastic agent is selected from the group consisting essentially of anti-microtubule agents, platinum coordination complexes, alkylating agents, antibiotic agents, topoisomerase II inhibitors, antimetabolites, topoisomerase I inhibitors, hormones and hormonal analogues, signal transduction pathway inhibitors; non-receptor

tyrosine kinase angiogenesis inhibitors; immunotherapeutic agents; proapoptotic agents; and cell cycle signaling inhibitors.

18. The method of claim 16, wherein the at least one anti-neoplastic agent is an anti-microtubule agent selected from diterpenoids and vinca alkaloids.

19. The method of claim 16, wherein the at least one anti-neoplastic agent is a diterpenoid.

20. The method of claim 16, wherein the at least one anti-neoplastic agent is a vinca alkaloid.

21. The method of claim 16, wherein the at least one anti-neoplastic agent is a platinum coordination complex.

22. The method of claim 16, wherein the at least one anti-neoplastic agent is paclitaxel, carboplatin, or vinorelbine.

23 The method of claim 16, wherein the at least one anti-neoplastic agent is paclitaxel.

24. The method of claim 16, wherein the at least one anti-neoplastic agent is carboplatin.

25. The method of claim 16, wherein the at least one anti-neoplastic agent is vinorelbine.

26. The method of claim 16, wherein the at least one anti-neoplatic agent is a signal transduction pathway inhibitor.

27. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a growth factor receptor kinase selected from the group consisting of VEGFR2, TIE2, PDGFR, BTK, IGFR-1, TrkA, TrkB, TrkC, and c-fms.

28. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of rafk, akt, and PKC-zeta.

29. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the src family of kinases.

30. The method of claim 29, wherein the signal transduction pathway inhibitor is an inhibitor of c-src.

31. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of Ras oncogene selected from inhibitors of farnesyl transferase and geranylgeranyl transferase.

32. The method of claim 26, wherein the signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the group consisting of PI3K.

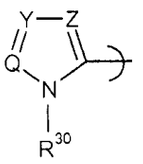
33. The method of claim 16, wherein the at least one anti-neoplastic agent is a cell cycle signaling inhibitor.

34. The method of claim 33, wherein the cell cycle signaling inhibitor is selected from inhibitors of the group CDK2, CDK4, and CDK6.

35. A pharmaceutical combination as claimed in claim 16 for use in therapy.

36. The use of a pharmaceutical combination as claimed in claim 16 for the preparation of a medicament useful in the treatment of cancer.

37. A compound of Formula (I), as defined in Claim 1, wherein:
R^{41} is selected from: chlorine, ethyl, methyl and methoxy;

R^{42} is  ,

where Q is nitrogen, Y is –CH- and Z is $-C(R^{48})-$, and

R^{30} is selected from methyl and ethyl,

where R^{48} is selected from: hydrogen, methyl, chlorine and bromine;

R^{43} is hydrogen;

R^{44} is $-CH_2$-phenyl wherein the phenyl is substituted by one or two substituents selected from fluorine and trifluoromethyl;

R^{45} is hydrogen;

R^{20} is hydrogen;

X is selected from O and S; and

n is 1;

and/or a pharmaceutically acceptable salt thereof.

38. The method according to claim 7 wherein said cancer is selected from: brain (gliomas), glioblastomas, Bannayan-Zonana syndrome, Cowden disease, Lhermitte-Duclos disease, breast, inflammatory breast cancer, Wilm's tumor, Ewing's sarcoma, Rhabdomyosarcoma, ependymoma, medulloblastoma, colon, head and neck, kidney, lung, liver, melanoma, ovarian, pancreatic, prostate, sarcoma, osteosarcoma, giant cell tumor of bone, thyroid, Lymphoblastic T cell leukemia, Chronic myelogenous leukemia, Chronic lymphocytic leukemia, Hairy-cell leukemia, acute lymphoblastic leukemia, acute myelogenous leukemia, Chronic neutrophilic leukemia, Acute lymphoblastic T cell

leukemia, Plasmacytoma, Immunoblastic large cell leukemia, Mantle cell leukemia, Multiple myeloma Megakaryoblastic leukemia, multiple myeloma, acute megakaryocytic leukemia, promyelocytic leukemia, Erythroleukemia,

malignant lymphoma, hodgkins lymphoma, non-hodgkins lymphoma, lymphoblastic T cell lymphoma, Burkitt's lymphoma, follicular lymphoma,

neuroblastoma, bladder cancer, urothelial cancer, lung cancer, vulval cancer, cervical cancer, endometrial cancer, renal cancer, mesothelioma, esophageal cancer, salivary gland cancer, hepatocellular cancer, gastric cancer, nasopharangeal cancer, buccal cancer, cancer of the mouth, GIST (gastrointestinal stromal tumor) and testicular cancer.

39. The method of claim 38 wherein the mammal is a human.

40. A compound of claim 3 selected from:

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-(2-amino-1-phenylethyl)-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-{[(2Z)-1-methyl-2-(2-propen-1-ylidene)hydrazino]methyl}-2-thiophenecarboxamide;

N-(2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-[2-amino-1-(phenylmethyl)ethyl]-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-(2-amino-1-phenylethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-bromo-5-(1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide; and

N-[2-amino-1-(phenylmethyl)ethyl]-4-methyl-5-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

and/or a pharmaceutically acceptable salt thereof.

41. A compound of claim 1 selected from:

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1H-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-ethyl-2-thiophenecarboxamide;

N-((1S)-2-amino-1-{[2-(trifluoromethyl)phenyl]methyl}ethyl)-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-((1*S*)-2-amino-1-{[3-(trifluoromethyl)phenyl]methyl}ethyl)-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-4-(4-bromo-1-methyl-1*H*-pyrazol-5-yl)-5-chloro-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-(methyloxy)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(4-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(1,4-dimethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide; and

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-ethyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

and/or a pharmaceutically acceptable salt thereof.

42. A compound of claim 1 selected from:

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-2-furancarboxamide;

N-{(1*S*)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-thiophenecarboxamide;

N-{(1*S*)-2-amino-1-[(3,4-difluorophenyl)methyl]ethyl}-5-chloro-4-(4-chloro-1-methyl-1*H*-pyrazol-5-yl)-2-furancarboxamide;

and/or a pharmaceutically acceptable salt thereof.

INHIBIDORES DE LA ACTIVIDAD DE Akt

CAMPO DE LA INVENCIÓN

Esta invención se refiere a nuevos compuestos de carboxamida heterocíclicos y al uso de tales compuestos como inhibidores de la actividad de la proteína quinasa B (en lo sucesivo, PKB/Akt, PKB o Akt) y en el tratamiento de cáncer y artritis.

ANTECEDENTES DE LA INVENCIÓN

La presente invención se refiere a compuestos heterocíclicos que contienen carboxamida que son inhibidores de la actividad de una o más de las isoformas de la serina/treonina quinasa, Akt (también conocida como proteína quinasa B); adecuadamente los compuestos de la invención son inhibidores de la actividad de las tres isoformas de la serina/treonina quinasa, Akt. La presente invención también se refiere a composiciones farmacéutuicas que comprenden tales compuestos y a métodos de uso de los compuestos de la presente invención en el tratamiento de cáncer y artritis (Liu et al. Current Opin. Pharmacology 3:317-22 (2003)).

La apoptosis (muerte celular programada) juega papeles esenciales en el desarrollo embrionario y en la patogénesis de diversas enfermedades tales como enfermedades neuronales degenerativas, enfermedades cardiovasculares y cáncer. Un trabajo reciente ha conducido a la identificación de diversos productos génicos pro- y anti-apoptóticos que están implicados en la regulación o ejecución de la muerte celular programada. La expresión de genes anti-apoptóticos, tales como Bcl2 o Bcl-x_L, inhibe la muerte celular apoptótica inducida por diversos estímulos. Por otra parte, la expresión de genes pro-apoptóticos, tales como Bax o Bad, conduce a la muerte celular programada (Adams et al. *Science,* 281:1322-1326 (1998)). La ejecución de la muerte celular programada está mediada por proteinasas relacionadas con la caspasa-1, incluyendo la caspasa-3, caspasa-7, caspasa-8 y caspasa-9 etc. (Thornberry et al. *Science,* 281:1312-1316 (1998)).

La ruta de la fosfatidilinositol 3'-OH quinasa (PI3K)/Akt/PKB parece importante para regular la supervivencia celular/muerte celular (Kulik et al. *Mol.Cell.Biol.* 17:1595-1606 (1997); Franke et al, *Cell,* 88:435-437 (1997); Kauffmann-Zeh et al. *Nature* 385:544-548 (1997) Hemmings *Science,* 275:628-630 (1997); Dudek et al., *Science,* 275:661-665 (1997)). Ciertos factores de supervivencia, tales como el factor de crecimiento derivado de plaquetas (PDGF),

el factor de crecimiento nervioso (NGF) y el factor de crecimiento semejante a insulina-1 (IGF-I), promueven la supervivencia celular en diversas condiciones induciendo la actividad de PI3K (Kulik et al. 1997, Hemmings 1997). La PI3K activada conduce a la producción de fosfatidilinositol (3,4,5)-trifosfato (PtdIns (3,4,5)-P3) que, a su vez, se une y promueve la activación de la serina/treonina quinasa Akt, que contiene un dominio de homología a pleckstrina (PH) (Franke et al *Cell,* 81:727-736 (1995); Hemmings *Science,* 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998), Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Los inhibidores específicos de PI3K o mutantes de Akt/PKB dominantes negativos anulan las actividades promotoras de la supervivencia de estos factores de crecimiento o citoquinas. Se ha descrito previamente que los inhibidores de PI3K (LY294002 o wortmanina) bloqueaban la activación de Akt/PKB por quinasas corriente arriba. Además, la introducción de mutantes de PI3K o Akt/PKB constitutivamente activos promueve la supervivencia celular en condiciones en las que las células normalmente experimentan muerte celular apoptótica (Kulik et al. 1997, Dudek et al. 1997).

El análisis de los niveles de Akt en tumores humanos demostró que Akt2 se sobreexpresa en un número significativo de cánceres de ovario (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) y páncreas (J. Q. Cheung *et al. Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). De igual forma, se descubrió que Akt3 se sobreexpresa en líneas de cáncer de mama y de próstata (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999)). Se demostró que Akt-2 se sobreexpresaba en 12% de los carcinomas de ovario y que la amplificación de Akt era especialmente frecuente en 50% de los tumores indiferenciados, lo cual sugería que Akt también puede estar asociada con la agresividad de los tumores (Bellacosa, e*t al., Int. J. Cancer*, 64, páginas 280-285, 1995). Se ha notificado una mayor actividad quinasa Akt1 en cánceres de mama, ovario y próstata (Sun *et al. Am. J. Pathol. 159:* 431-7 (2001)).

El supresor tumoral PTEN, una fosfatasa de proteínas y lípidos que elimina específicamente el 3' fosfato de PtdIns(3,4,5)-P3, es un regulador negativo de la ruta PI3K/Akt (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Nati. Acad. Sci. U.S.A.* 96:6199-6204 (1999)). Ciertas mutaciones en la línea germinal de PTEN son responsables de síndromes de cáncer humano tales como la enfermedad de Cowden (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN está delecionado en un gran porcentaje de tumores

humanos y las líneas de células tumorales sin PTEN funcional muestran niveles elevados de Akt activada (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

Estas observaciones demuestran que las rutas de PI3K/Akt juegan papeles importantes para regular la supervivencia celular o la apoptosis en la tumorigénesis.

Se han identificado tres miembros de la subfamilia Akt/PKB de serina/treonina proteína quinasas reguladas por segundos mensajeros y se han denominado Akt1/ PKBα, Akt2/PKBβ y Akt3/PKBγ respectivamente. Las isoformas son homólogas, particularmente en regiones que codifican los dominios catalíticos. Las Akt/PKB se activan por sucesos de fosforilación que se producen en respuesta a la señalización de PI3K. La PI3K fosforila fosfolípidos de inositol de la membrana, generando los segundos mensajeros fosfatidil-inositol 3,4,5-trifosfato y fosfatidilinositol 3,4-bisfosfato que, como se ha demostrado, se unen al dominio PH de Akt/PKB. El modelo actual de activación de Akt/PKB propone el reclutamiento de la enzima en la membrana por fosfoinosítidos 3'-fosforilados, con lo que se produce la fosforilación de los sitios reguladores de Akt/PKB por las quinasas corriente arriba (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

La fosforilación de Akt1/PKBα tiene lugar en dos sitios reguladores, Thr^{308} en el bucle de activación del dominio catalítico y en la Ser^{473} cerca del extremo carboxi (D. R. Alessi *et al. EMBO J.* 15:6541-6551 (1996) y R. Meier *et al. J. Biol. Chem.* 272:30491-30497 (1997)). Existen sitios de fosforilación reguladora equivalentes en Akt2/PKBβ y Akt3/PKBγ. Se ha clonado la quinasa corriente arriba, que fosforila Akt/PKB en el sitio del bucle de activación y se ha denominado proteína quinasa 1 dependiente de 3'-fosfoinosítido (PDK1). La PDK1 no sólo fosforila Akt/PKB, sino también la quinasa S6 ribosomal p70, p90RSK, la quinasa sérica y regulada por glucocorticoides (SGK) y la proteína quinasa C. Aún no se ha identificado la quinasa corriente arriba que fosforila el sitio regulador de Akt/PKB cerca del extremo carboxi, pero ciertos informes recientes implican un papel para la quinasa asociada a integrina (ILK-1), una proteína serina/treonina quinasa, o autofosforilación.

La inhibición de la activación y la actividad de Akt puede conseguirse inhibiendo PI3K con inhibidores tales como LY294002 y wortmanina. Sin embargo, la inhibición de PI3K puede afectar indiscriminadamente no sólo a las tres isozimas

Akt, sino también a otras moléculas de señalización que contienen el dominio PH que son dependientes de PdtIns(3,4,5)-P3, tales como la familia Tec de tirosina quinasas. Además, se ha descrito que Akt puede activarse por señales de crecimiento que son independientes de PI3K.

Como alternativa, la actividad Akt puede inhibirse bloqueando la actividad de la quinasa corriente arriba PDK1, El compuesto UCN-01, según se ha publicado, es un inhibidor de PDK1, *Biochem. J.* 375(2):255 (2003). De nuevo, la inhibición de PDK1 daría como resultado la inhibición de múltiples proteína quinasas cuyas actividades dependen de PDK1, tales como las isoformas atípicas de PKC, SGK, y quinasas S6 (Williams et al. *Curr. Biol.* 10:439-448 (2000)).

Los inhibidores de Akt de molécula pequeña son útiles en el tratamiento de tumores, especialmente los asociados con Akt activada (por ejemplo, tumores sin función PTEN y tumores con mutaciones ras). PTEN es un regulador negativo crítico de Akt y su función se pierde en muchos cánceres, incluyendo los carcinomas de mama y de próstata, glioblastomas, y varios síndromes asociados con cánceres incluyendo el síndrome de Bannayan-Zonana (Maehama, T. *et al. Annual Review of Biochemistry*, *70*: 247 (2001)), la enfermedad de Cowden (Parsons, R.; Simpson, L. *Methods en Molecular Biology (Totowa, NJ, United States), 222 (Tumor Suppressor Genes, Volume 1)*: 147 (2003)), y la enfermedad de Lhermitte-Duclos (Backman, S. *et al. Current Opinion en Neurobiology*, *12(5)*: 516 (2002)). Akt3 está regulada positivamente en cánceres de mama con deficiencia en receptores de estrógenos y en líneas celulares de cánceres de próstata independientes de andrógenos y Akt2 está sobreexpresada en carcinomas pancreáticos y de ovario. Akt1 está amplificada en cánceres gástricos (Staal, *Proc. Natl. Acad. Sci.* USA *84*: 5034-7 (1987) y está regulada positivamente en cánceres de mama (Stal *et al. Breast Cancer Res. 5*: R37-R44 (2003)). Por lo tanto, es de esperar que un inhibidor de Akt de pequeña molécula sea útil para el tratamiento de estos tipos de cáncer así como de otros tipos de cáncer. Los inhibidores de Akt también son útiles en combinación con otros agentes quimioterapéuticos y anticancerosos adicionales.

Es un objeto de la presente invención proporcionar nuevos compuestos que sean inhibidores de Akt/PKB.

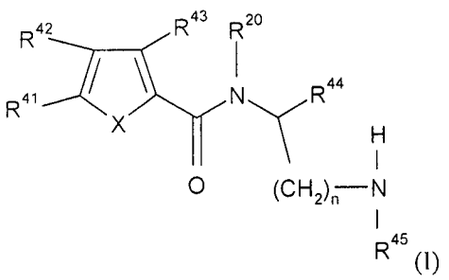
También es un objeto de la presente invención proporcionar composiciones farmacéuticas que comprenden un vehículo farmacéutico y compuestos útiles en los métodos de la invención.

También es un objeto de la presente invención proporcionar un método para tratar cáncer que comprende administrar tales inhibidores de la actividad de Akt/PKB.

También es un objeto de la presente invención proporcionar un método para tratar artritis que comprende administrar tales inhibidores de la actividad de Akt/PKB.

SUMARIO DE LA INVENCIÓN

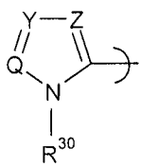
Esta invención se refiere a nuevos compuestos de Fórmula (I):



(I)

donde:

R^{41} y R^{42} se seleccionan independientemente entre: hidrógeno,



, halógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, alquiloxi C_{1-4}, alquiloxi C_{1-4} sustituido, furano, furano sustituido, tiofeno y tiofeno sustituido,

donde Q y Y se seleccionan independientemente entre: nitrógeno y $-C(R^{70})-$, y Z se selecciona entre: nitrógeno y $-C(R^{48})-$, con la condición de que al menos uno y como mucho 2 de Q, Y y Z son nitrógeno, y R^{30} se selecciona entre: alquilo C_{1-4} y alquilo C_{1-4} sustituido con uno a tres átomos de flúor,

donde R^{70} se selecciona entre: hidrógeno, y halógeno, y

R^{48} se selecciona entre: hidrógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido y halógeno;

R^{43} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, alquiloxi C_{1-4}, alquiloxi C_{1-4} sustituido, furano y tiofeno;

R^{44} está ausente o se selecciona entre: $-(CR^{60}R^{61})_mAR$ donde el grupo AR está sin sustituir, $-(CR^{60}R^{61})_mAR$ donde el grupo AR está sustituido y alquilo C_{1-6},

donde m es de 0 a 3 y AR es un anillo, aromático o no aromático, saturado o insaturado, cíclico o policíclico, que contiene de 3 a 16 átomos de carbono y que contiene opcionalmente de uno a tres heteroátomos, con la condición de que cuando el anillo es aromático y el número de átomos de carbono es 3, el anillo contenga al menos dos heteroátomos y cuando el anillo es aromático y el número de átomos de carbono es 4, el anillo contenga al menos un heteroátomo, y

R^{60} y R^{61} se seleccionan independientemente entre: hidrógeno y alquilo C_{1-4}, con la condición de que cuando m es 3, no más de 4 de R^{60} y R^{61}, cuando se añaden juntos, sean alquilo C_{1-4},

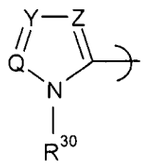
R^{45} se selecciona entre hidrógeno y alquilo C_{1-4};

R^{20} se selecciona entre hidrógeno, alquilo C_{1-4} e hidroxi;

X se selecciona entre O, S y NR^{49},

donde R^{49} se selecciona entre hidrógeno y alquilo C_{1-4}; y

n es de 0 a 2 y este resto está opcionalmente, si es aplicable, sustituido con hidroxialquilo C_{1-4};

con la condición de que uno y sólo uno de R^{41} y R^{42} sea  ;

y/o sales farmacéuticamente aceptables de los mismos.

Esta invención se refiere a un método para tratar el cáncer, que comprende administrar a un sujeto que lo necesita una cantidad eficaz de un compuesto inhibidor de Akt/PKB de Fórmula (I).

Esta invención se refiere a un método para tratar la artritis, que comprende administrar a un sujeto que lo necesita una cantidad eficaz de un compuesto inhibidor de Akt/PKB de Fórmula (I).

La presente invención también se refiere al descubrimiento de que los compuestos de Fórmula (I) son activos como inhibidores de Akt/PKB.

En otro aspecto de la invención se proporcionan nuevos procesos y nuevos intermedios útiles en la preparación de los compuestos inhibidores de Akt/PKB de la presente invención.

En la presente invención se incluyen composiciones farmacéuticas que comprenden un vehículo farmacéutico y compuestos útiles en los métodos de la invención.

En la presente invención también se incluyen métodos de co-administración de los compuestos inhibidores de Akt/PKB de la presente invención con otros ingredientes activos.

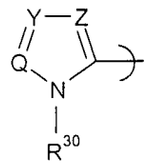
DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Esta invención se refiere a compuestos de fórmula (I) como se ha descrito anteriormente.

Los compuestos de Fórmula (I) de la presente invención inhiben la actividad de Akt/PKB. En particular, los compuestos descritos en este documento inhiben cada una de las tres isoformas de Akt/PKB.

Entre los compuestos de Fórmula (I) de la presente invención están aquellos en los que:

R^{41} y R^{42} se seleccionan independientemente entre: hidrógeno,



, halógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, alquiloxi C_{1-4}, alquiloxi C_{1-4} sustituido, furano, furano sustituido, tiofeno y tiofeno sustituido,

donde Q es nitrógeno, Y se selecciona entre: nitrógeno y $-C(R^{70})-$, y Z se selecciona entre: nitrógeno y $-C(R^{48})-$, con la condición de que como máximo uno de Y y Z sea nitrógeno, y R^{30} se selecciona entre: alquilo C_{1-4} y alquilo C_{1-4} sustituido con uno a tres átomos de flúor,

donde R^{70} se selecciona entre: hidrógeno, y halógeno, y

R^{48} se selecciona entre: hidrógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido y halógeno;

R^{43} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, alquiloxi C_{1-4}, alquiloxi C_{1-4} sustituido, furano y tiofeno;

R^{44} está ausente o se selecciona entre: $-(CR^{60}R^{61})_mAR$ donde el grupo AR está sin sustituir, $-(CR^{60}R^{61})_mAR$ donde el grupo AR está sustituido y alquilo C_{1-6},

donde m es de 0 a 3 y AR es un anillo, aromático o no aromático, saturado o insaturado, cíclico o policíclico, que contiene de 3 a 16 átomos de carbono y que contiene opcionalmente de uno a tres

heteroátomos, con la condición de que cuando el anillo es aromático y el número de átomos de carbono es 3, el anillo contenga al menos dos heteroátomos y cuando el anillo es aromático y el número de átomos de carbono es 4, el anillo contenga al menos un heteroátomo, y

R^{60} y R^{61} se seleccionan independientemente entre: hidrógeno y alquilo C_{1-4}, con la condición de que cuando m es 3, no más de 4 de R^{60} y R^{61}, cuando se añaden juntos, sean alquilo C_{1-4},

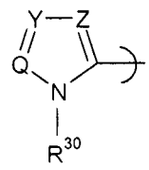
R^{45} se selecciona entre hidrógeno y alquilo C_{1-4};

R^{20} se selecciona entre hidrógeno, alquilo C_{1-4} e hidroxi;

X se selecciona entre O, S y NR^{49},

donde R^{49} se selecciona entre hidrógeno y alquilo C_{1-4}; y

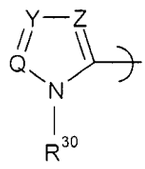
n es de 0 a 2 y este resto está opcionalmente, si es aplicable, sustituido con hidroxialquilo C_{1-4};

con la condición de que uno y sólo uno de R^{41} y R^{42} sea 

;

y/o sales farmacéuticamente aceptables de los mismos.

Entre los compuestos de Fórmula (I) de la presente invención están aquellos en los que:

R^{41} y R^{42} se seleccionan independientemente entre: hidrógeno, 

, halógeno, alquilo C_{1-4}, trifluorometilo, metoxi, furano y tiofeno,

donde Q es nitrógeno, Y se selecciona entre: nitrógeno y $-C(R^{70})-$, y Z se selecciona entre: nitrógeno y $-C(R^{48})-$, con la condición de que como máximo uno de Y y Z sea nitrógeno, y R^{30} sea alquilo C_{1-4},

donde R^{70} se selecciona entre: hidrógeno, y halógeno, y

R^{48} se selecciona entre: hidrógeno, alquilo C_{1-4}, trifluorometilo, arilo, heteroarilo, cicloalquilo, heterocicloalquilo y halógeno;

R^{43} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4} y metoxi;

R^{44} está ausente o se selecciona entre: $-(CR^{60}R^{61})_mAAR$ donde el grupo AAR está sin sustituir, $-(CR^{60}R^{61})_mAAR$ donde el grupo AAR está sustituido y alquilo C_{1-6},

donde m es de 0 a 3 y AAR se selecciona entre fenilo, indol, naftaleno, piridina y ciclohexilo, y

R^{60} y R^{61} se seleccionan independientemente entre: hidrógeno y metilo, con la condición de que cuando m es 3 no más de 4 de R^{60} y R^{61}, cuando se añaden juntos, sean metilo,

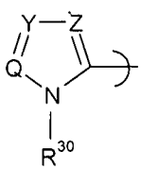
R^{45} se selecciona entre hidrógeno y alquilo C_{1-4};

R^{20} se selecciona entre hidrógeno, metilo e hidroxi;

X se selecciona entre O, S y NR^{49},

donde R^{49} se selecciona entre hidrógeno y metilo; y

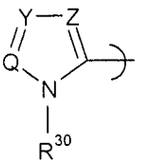
n es de 1 a 2 y este resto está opcionalmente sustituido con hidroxilmetilo;

con la condición de que uno y sólo uno de R^{41} y R^{42} sea 

;

y/o sales farmacéuticamente aceptables de los mismos.

Entre los compuestos de Fórmula (I) de la presente invención están aquellos en los que:

R^{41} y R^{42} se seleccionan independientemente entre: hidrógeno,  , halógeno, alquilo C_{1-4}, trifluorometilo, metoxi y furano,

donde Q es nitrógeno, Y se selecciona entre: nitrógeno y $-C(R^{70})-$, y Z se selecciona entre: nitrógeno y $-C(R^{48})-$, con la condición de que como máximo uno de Y y Z sea nitrógeno, y R^{30} sea alquilo C_{1-4},

donde R^{70} se selecciona entre: hidrógeno, y halógeno, y

R^{48} se selecciona entre: hidrógeno, alquilo C_{1-4}, trifluorometilo, fenilo, ciclopropilo y halógeno;

R^{43} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4} y metoxi;

R^{44} está ausente o se selecciona entre: $-(CR^{60}R^{61})_mAAR$ donde el grupo AAR está sin sustituir, $-(CR^{60}R^{61})_mAAR$ donde el grupo AAR está sustituido y alquilo C_{1-6},

donde m es de 0 a 3 y AAR se selecciona entre fenilo, indol, naftaleno, piridina y ciclohexilo, y

R^{60} y R^{61} se seleccionan independientemente entre: hidrógeno y metilo, con la condición de que cuando m es 3 no más de 4 de R^{60} y R^{61}, cuando se añaden juntos, sean metilo,

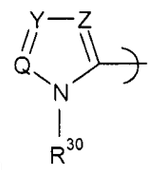
R^{45} se selecciona entre hidrógeno y alquilo C_{1-4};

R^{20} se selecciona entre hidrógeno, metilo e hidroxi;

X se selecciona entre O, S y NR^{49},

donde R^{49} se selecciona entre hidrógeno y metilo; y

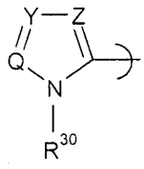
n es de 1 a 2 y este resto está opcionalmente sustituido con hidroxilmetilo;

con la condición de que uno y sólo uno de R^{41} y R^{42} sea  ;

y/o sales farmacéuticamente aceptables de los mismos.

Entre los compuestos de Fórmula (I) de la presente invención están aquellos en los que:

R^{41} se selecciona entre: cloro, etilo, metilo y metoxi;

R^{42} es  ,

donde Q es nitrógeno, Y es –CH- y Z es $-C(R^{48})-$, y

R^{30} se selecciona entre metilo y etilo,

donde R^{48} se selecciona entre: hidrógeno, metilo, cloro y bromo;

R^{43} es hidrógeno;

R^{44} es $-CH_2$-fenilo donde el grupo fenilo está sustituido con uno o dos sustituyentes seleccionados entre flúor y trifluorometilo;

R^{45} es hidrógeno;

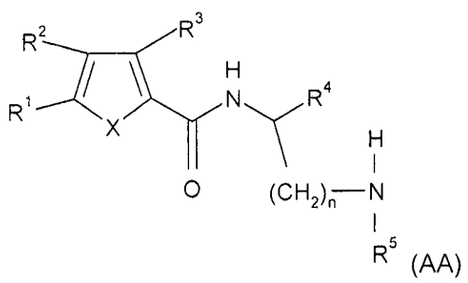
R^{20} es hidrógeno;

X se selecciona entre O y S; y

n es 1;

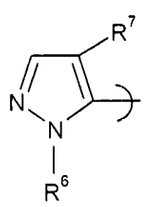
y/o sales farmacéuticamente aceptables de los mismos.

En los compuestos de Fórmula (I) de la presente invención se incluyen compuestos de Fórmula (AA):



(AA)

donde:

R^1 y R^2 se seleccionan independientemente entre: hidrógeno, halógeno, alquilo C_{1-4}, furano y tiofeno,  ,

donde R^6 es alquilo C_{1-4} y R^7 se selecciona entre hidrógeno, alquilo C_{1-4} y halógeno;

R^3 se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4}, furano y tiofeno;

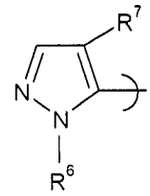
R^4 se selecciona entre $-(CH_2)_m$arilo y $-(CH_2)_m$arilo donde el arilo está sustituido,

donde m es de 0 a 2;

R^5 se selecciona entre hidrógeno y alquilo C_{1-4};

X se selecciona entre O y S; y

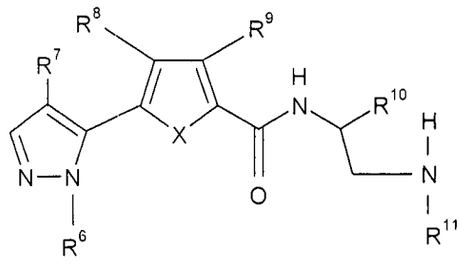
n es de 0 a 2;



con la condición de que uno y sólo uno de R^1 y R^2 sea y con la condición adicional de que al menos uno de R^1, R^2 y R^3 sea hidrógeno;

y/o sales farmacéuticamente aceptables de los mismos.

En los compuestos de Fórmula (I) de la presente invención se incluyen compuestos de Fórmula (BB):



(BB)

donde:

R^8 y R^9 se seleccionan independientemente entre: hidrógeno, halógeno, alquilo C_{1-4}, furano y tiofeno;

R^6 es alquilo C_{1-4};

R^7 se selecciona entre hidrógeno, alquilo C_{1-4} y halógeno;

R^{10} se selecciona entre: $-(CH_2)_m$arilo C_5-C_{12} y $-(CH_2)_m$arilo C_5-C_{12} donde el arilo está sustituido,
donde m es de 0 a 2;

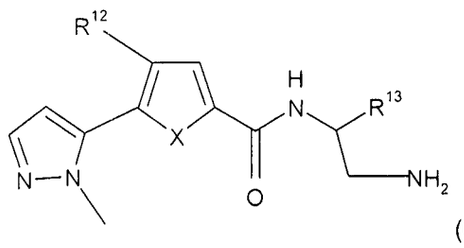
R^{11} se selecciona entre hidrógeno y alquilo C_{1-4};

X se selecciona entre O y S; y

con la condición de que al menos uno de R^8 y R^9 sea hidrógeno;

y/o sales farmacéuticamente aceptables de los mismos.

En los compuestos de Fórmula (I) de la presente invención se incluyen compuestos de Fórmula (CC):



(CC)

donde:

R^{12} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4}, furano y tiofeno;

R^{13} se selecciona entre: $-(CH_2)_m$fenilo y $-(CH_2)_m$fenilo donde el grupo fenilo está sustituido,
donde m es de 0 a 2;

X se selecciona entre O y S; y

y/o sales farmacéuticamente aceptables de los mismos.

Entre los compuestos útiles de la presente invención se incluyen:

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-(2-amino-1-feniletil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida;

N-(2-amino-1-feniletil)-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida;

N-(2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-(2-amino-1-feniletil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(3-furanil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[3-amino-1-(fenilmetil)propil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

4-bromo-N-[2-(metilamino)-1-feniletil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-cloro-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-bromo-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[1-(aminometil)-3-fenilpropil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[1-(aminometil)-3-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

4-bromo-*N*-[3-(metilamino)-1-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[3-(metilamino)-1-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

4-bromo-*N*-[2-(metilamino)-1-(fenilmetil)etil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

N-((1*S*)-2-amino-1-{[4-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[1-(aminometil)-2-metil-2-fenilpropil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida;

N-[2-amino-1-(fenilmetil)etil]-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida;

N-[2-amino-1-(fenilmetil)etil]-1-metil-4-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-(metilamino)-1-(fenilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-*N*-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[1-(aminometil)-2-metil-2-fenilpropil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[4-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-imidazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-clorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(1*H*-indol-3-ilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-clorofenil)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(1-naftalenil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(1-naftalenil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{2-amino-1-[2-(trifluorometil)fenil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{2-amino-1-[2-(trifluorometil)fenil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-clorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-(3-amino-1-fenilpropil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-*N*-hidroxi-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-fluoro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,6-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(3-piridinilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*R*)-2-amino-1-feniletil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(3-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(2-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-[2-amino-1-(2-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(3-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-(2-aminoetil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-metiletil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[3-(trifluorometil)fenil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-[(1*S*)-1-(aminometil)-3-metilbutil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

(*N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dietil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-1,2,3-triazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*,2*S*)-2-amino-3-hidroxi-1-fenilpropil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida; y

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

y/o sales farmacéuticamente aceptables de los mismos.

Los compuestos de fórmula (I) se incluyen en las composiciones farmacéuticas de la invención y se usan en los métodos de la invención.

Ciertos de los compuestos descritos en este documento pueden contener uno o más átomos quirales, o pueden existir de otra manera en forma de dos enantiómeros. Por consiguiente, los compuestos de esta invención incluyen mezclas de enantiómeros así como enantiómeros purificados o mezclas enantioméricamente enriquecidas. Además, se entiende que todos los tautómeros y mezclas de tautómeros se incluyen dentro del alcance de los compuestos de Fórmula (I).

Ciertos compuestos descritos en este documento pueden formar un solvato que se entiende que es un complejo de estequiometría variable formado por un soluto (en esta invención, un compuesto de Fórmula I o una sal del mismo) y un disolvente. Estos disolventes, para los fines de la invención, no pueden interferir con la actividad biológica del soluto. Los ejemplos de disolventes adecuados incluyen, pero sin limitación, agua, metanol, etanol y ácido acético. Preferiblemente, el disolvente usado es un disolvente farmacéuticamente aceptable. Los ejemplos de disolventes farmacéuticamente aceptables adecuados incluyen, sin limitación, agua, etanol y ácido acético. Más preferiblemente, el disolvente usado es agua.

Por el término "arilo", y derivados del mismo, usado solo o como parte de un resto mayor como en "–$(CH_2)_m$arilo", como se usa en este documento, a menos que se defina otra cosa, se entienden sistemas de anillos monocíclicos, bicíclicos y tricíclicos que tienen un total de cinco a catorce miembros de anillo, donde al menos un sistema de anillos es aromático y donde cada anillo del sistema contiene de 3 a 7 miembros, tal como fenilo, naftaleno, tetrahidronaftaleno y bifenilo.

Adecuadamente, por el término "arilo" se entiende un sistema de anillos aromáticos monocíclicos que tiene un total de cinco a 7 miembros de anillo.

Por el término "heteroarilo", y derivados del mismo, usado solo o como parte de un resto mayor como en "–$(CH_2)_m$heteroarilo", como se usa en este documento, a menos que se defina otra cosa, se entiende un anillo aromático cíclico que contiene de 3 a 7 átomos de carbono y que contiene de uno a 3 heteroátomos, con la condición de que cuando el número de átomos de carbono sea 3, el anillo aromático contenga al menos dos heteroátomos. Los grupos "heteroarilo" ejemplares incluyen piridina e indol.

Por el término "cicloalquilo", y derivados del mismo, usado solo o como parte de un resto mayor como en "–$(CH_2)_m$cicloalquilo", como se usa en este documento, a menos que se defina otra cosa, se entiende un anillo de hidrocarburo cíclico, no aromático, que tiene de tres a siete átomos de carbono. Los grupos "cicloalquilo" ejemplares incluyen ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo.

Por el término "heterocicloalquilo", y derivados del mismo, usado solo o como parte de un resto mayor como en "–$(CH_2)_m$heterocicloalquilo", como se usa en este documento, a menos que se defina otra cosa, se entiende un anillo de hidrocarburo cíclico, no aromático, que tiene de tres a seis átomos de carbono y que contiene 1 ó 2 heteroátomos. Los grupos "cicloalquilo" ejemplares incluyen piperazina y pirrolidina.

Por el término "arilo C_5-C_{12}", usado solo o como parte de un resto mayor como en "–$(CH_2)_m$arilo C_5-C_{12}", como se usa en este documento, se entiende un grupo aromático seleccionado entre: fenilo, naftaleno, tetrahidronaftanleno y bifenilo.

El término "sustituido", como se usa en este documento, a menos que se defina otra cosa, se refiere a que el resto químico objeto tiene de uno a cinco sustituyentes, adecuadamente de uno a tres sustituyentes, seleccionados entre el grupo que consiste en: $-CO_2R^{20}$, alquilo C_1-C_4, hidroxialquilo C_1-C_4, alquiloxi C_1-C_4, amino, alquilamino C_1-C_4, aminoalquilo C_1-C_4, dialquilamino C1-C4, hidroxi, nitro, tetrazol, ciano, oxo, halógeno y trifluorometilo, donde R^{20} se selecciona entre hidrógeno, alquilo C1-C4 y trifluorometilo.

Adecuadamente, el término "sustituido", como se usa en este documento, se refiere a que el resto químico objeto tiene de uno a tres sustituyentes, seleccionados entre el grupo que consiste en: alquilo C1-C4, hidroxialquilo C1-C4, alquiloxi C1-C4, amino, alquilamino C1-C4, aminoalquilo C1-C4, hidroxi, tetrazol, halógeno y trifluorometilo.

Adecuadamente, el término "sustituido", como se usa en este documento, se refiere a que el resto químico objeto tiene de uno a tres sustituyentes, seleccionados entre el grupo que consiste en: halógeno y trifluorometilo.

Mediante el término "heteroátomo" como se usa en este documento se pretende indicar oxígeno, nitrógeno o azufre.

Mediante el término "halógeno" como se usa en este documento se pretende indicar un sustituyente seleccionado entre bromuro, yoduro, cloruro y fluoruro.

Mediante el término "alquilo" y derivados del mismo y en todas las cadenas de carbonos como se usa en este documento, incluyendo las cadenas alquilo definidas por el término "$-(CH_2)_n$", "$-(CH_2)_m$" y similares, se pretende indicar una cadena de hidrocarburo saturada o insaturada, lineal o ramificada, y a menos que se indique lo contraro, la cadena carbonada contendrá de 1 a 12 átomos de carbono. Los ejemplos de alquilo, como se usa en este documento, incluyen: $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH(CH_3)_2$, $-CH_2-CH_2-C(CH_3)_3$, $-C\equiv C-C(CH_3)_3$, $-C(CH_3)_3$, $-(CH_2)_3-CH_3$, $-CH_2-CH(CH_3)_2$, $-CH(CH_3)-CH_2-CH_3$, $-CH=CH_2$ y $-C\equiv C-CH_3$.

Por el término "tratamiento" y derivados del mismo, como se usa en este documento, se entiende terapia profiláctica y terapéutica. La terapia profiláctica es apropiada, por ejemplo, cuando se considera que un sujeto está en alto riesgo de desarrollar cáncer, o cuando un sujeto se ha expuesto a un carcinógeno.

Como se usa en este documento, la expresión "cantidad eficaz" y derivados de la misma significa aquella cantidad de un profármaco o agente farmacéutico que provocará la respuesta biológica o médica de un tejido, sistema, animal o ser humano que se desea, por ejemplo, por un investigador o médico. Además, la expresión "cantidad terapéuticamente eficaz" y derivados de la misma significa cualquier cantidad que, comparada con un sujeto correspondiente que no ha recibido dicha cantidad, da como resultado un tratamiento mejorado, curación, prevención o mejoría de una enfermedad, trastorno o efecto secundario, o una disminución de la velocidad de avance de una enfermedad o trastorno. La expresión también incluye en su alcance cantidades eficaces para mejorar la función fisiológica normal.

Los compuestos de fórmula (I) se incluyen en las composiciones farmacéuticas de la invención y se usan en los métodos de la invención. Cuando está presente un grupo -COOH o -OH, pueden emplearse ésteres farmacéuticamente aceptables, por ejemplo metilo, etilo, pivaloiloximetilo, y

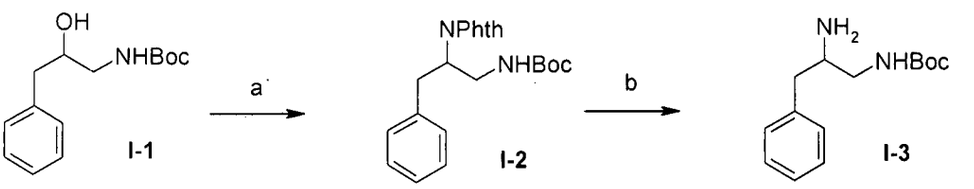
similares para -COOH, y acetato maleato y similares para -OH, y los ésteres conocidos en la técnica para modificar las características de solubilidad o hidrólisis, para su uso como formulaciones de liberación sostenida o de profármacos.

Las sales farmacéuticamente aceptables de los compuestos de la invención se preparan fácilmente por los especialistas en la técnica.

Los nuevos compuestos de Fórmulas (I), (AA), (BB) y (CC) se preparan en general como se muestra a continuación en los Esquemas 1 a 3, o por métodos análogos, con la condición de que los sustituyentes X y 'R' de las Fórmulas (I), (AA), (BB) y (CC), respectivamente, no incluyan ninguno de los sustituyentes que hacen inoperativos los procesos de cualquiera de los Esquemas 1 a 3. Todos los materiales de partida están disponibles en el mercado, o los expertos en la técnica pueden prepararlos con facilidad a partir de materiales de partida disponibles en el mercado.

Esquemas Generales

Esquema 1



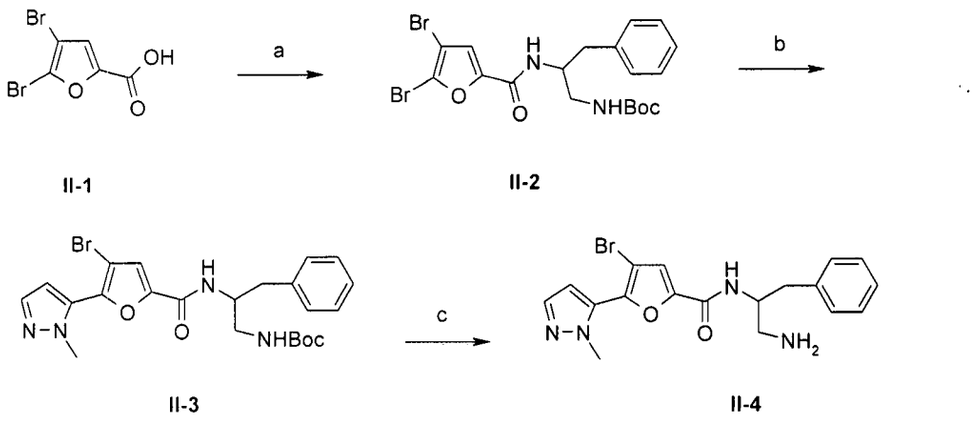
I-1 I-2 I-3

Reactivos: (a) Ftalimida, PPh_3, DEAD, THF, TA; (b) NH_2NH_2, MeOH, 50°C.

Se hizo reaccionar el amino alcohol (**I-1**) en condiciones de Mitsunobu para proporcionar la diamina diferencialmente protegida (**I-2**). Las reacciones de Mitsunobu son bien conocidas por los especialistas en la técnica de la síntesis orgánica. Los métodos y condiciones de reacción para tales transformaciones se analizan en *Synthesis* **1981**, 1-28. La desprotección selectiva del grupo ftalimida de (**I-2**) usando una amina nucleófila tal como hidrazina o metilamina en un disolvente polar tal como metanol, produjo la amina (**I-3**). Están disponibles muchos grupos protectores diferentes para un especialista en la técnica y pueden usarse aquí siempre que no interfieran con los procesos indicados en este documento. Los

métodos para la protección de aminas se describen en volúmenes de referencia convencionales, tales como Greene "Protective Groups in Organic Synthesis" (publicado por Wiley-Interscience).

Esquema 2

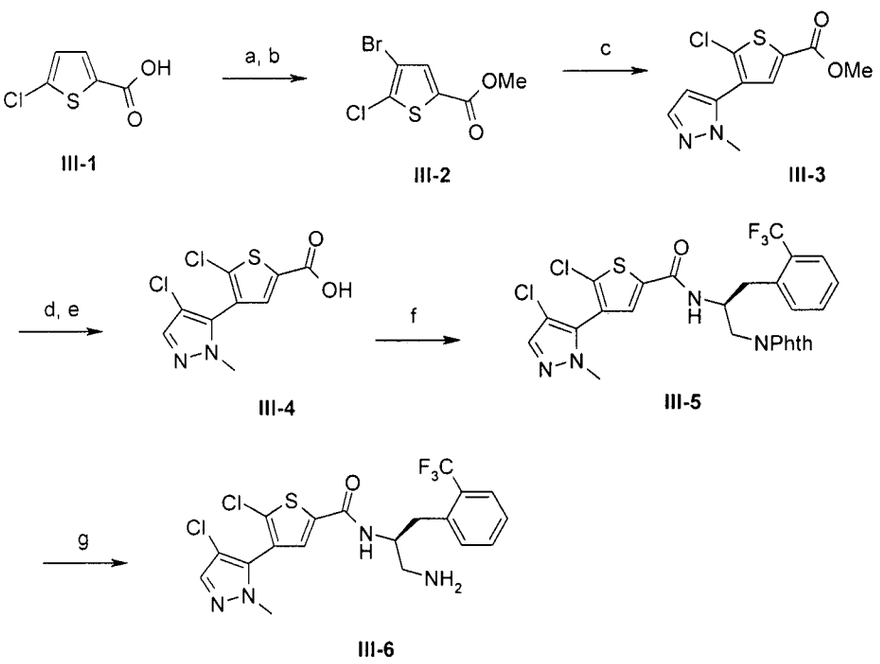


Reactivos: (a) PyBrop, $(i\text{-}Pr)_2NEt$, (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo, DCM, TA; (b) 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol, K_2CO_3, $Pd(PPh_3)_4$, dioxano/H_2O; (c) TFA/DCM, TA.

Se hizo reaccionar el ácido carboxílico (**II-1**) con (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo para formar la amida (**II-2**). En el mercado están disponibles una diversidad de reactivos de acoplamiento de amida tales como EDC, PyBrop, etc. Las reacciones de acoplamiento de amida se realizan en general en disolventes tales como DCM o DMF, utilizando una base orgánica tal como Et_3N o $(i\text{-}Pr)_2NEt$. El dibromuro (**II-2**) se acopló regioselectivamente con (2-{[(4,5-dibromo-2-furanil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo usando un procedimiento de acoplamiento de Suzuki. Los acoplamientos de tipo Suzuki se realizan típicamente usando un catalizador de paladio (0) tal como $Pd(PPh_3)_4$ con una base inorgánica, por ejemplo K_2CO_3, Na_2CO_3 o K_3PO_4, en una mezcla acuosa que contiene disolventes etéreos tales como DME, dioxano o THF. Los métodos para los acoplamientos mediados con paladio se describen en volúmenes de referencia convencionales, tales como Schlosser "Organometallics in Synthesis" (publicado por Wiley y sons). El tratamiento ácido de **II-3** con HCl o TFA

para retirar el grupo protector Boc produjo la amina (**II-4**). Están disponibles muchos grupos protectores diferentes para un especialista en la técnica y pueden usarse aquí siempre que no interfieran con los procesos indicados en este documento. Se describen métodos para la protección de aminas en volúmenes de referencia convencionales, tales como Greene "Protective Groups in Organic Synthesis" (publicado por Wiley-Interscience).

Esquema 3



Reactivos: (a) MeOH, H_2SO_4, 60°C; (b) $AlCl_3$, Br_2, $CHCl_3$; (c) 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol, K_2CO_3, $Pd_2(t\text{-}Bu)_3$, dioxano/H_2O, 70°C; (d) NCS, THF, 70°C; (e) NaOH 6 M, THF/MeOH, 50°C; (f) PyBrop, $(i\text{-}Pr)_2NEt$, 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona, DCM, TA; (g) NH_2NH_2, THF/MeOH, TA.

Se esterificó el ácido carboxílico (**III-1**) en condiciones de esterificación de Fisher convencionales y después se halogenó selectivamente con la ayuda de un ácido de Lewis para dar (**III-2**). El éster dihalogenado se acopló selectivamente con 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol usando química de

acoplamiento de Suzuki para dar (**III-3**). Los acoplamientos de tipo Suzuki se realizan típicamente usando un catalizador de paladio (0) tal como $Pd(PPh_3)_4$ con una base inorgánica, por ejemplo K_2CO_3, Na_2CO_3 o K_3PO_4, en una mezcla acuosa que contiene disolventes etéreos tales como DME, dioxano o THF. Se describen métodos para los acoplamientos mediados con paladio en volúmenes de referencia convencionales, tales como Schlosser "Organometallics in Synthesis" (publicado por Wiley y Sons). El éster (**III-3**) se cloró usando NCS y se saponificó *in situ* usando NaOH acuoso. El ácido carboxílico resultante (**III-4**) se acopló con 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona para formar la amida (**III-5**). En el mercado están disponibles una diversidad de reactivos de acoplamiento de amida tales como EDC, PyBrop, etc. Las reacciones de acoplamiento de amida se realizan en general en disolventes tales como DCM o DMF, utilizando una base orgánica tal como Et_3N o $(i\text{-}Pr)_2NEt$. La amida (**III-5**) se desprotegió usando hidrazina para dar la amina (**III-6**). Están disponibles muchos grupos protectores diferentes para un especialista en la técnica y pueden usarse aquí siempre que no interfieran con los procesos indicados en este documento. Se describen métodos para la protección de aminas en volúmenes de referencia convencionales, tales como Greene "Protective Groups in Organic Synthesis" (publicado por Wiley-Interscience).

Mediante el término "co-administrar" y derivados del mismo, como se usa en este documento, se pretende indicar la administración simultánea o cualquier manera de administración secuencial separada de un compuesto inhibidor de AKT, como se describe en este documento, y otro u otros ingredientes activos, considerados útiles en el tratamiento de cáncer, incluyendo quimioterapia y radioterapia, o útiles en el tratamiento de artritis. La expresión otro u otros ingredientes activos, como se usa en este documento, incluye cualquier compuesto o agente terapéutico conocido por o que demuestra propiedades ventajosas cuando se administra a un paciente en necesidad de tratamiento de cáncer o artritis. Preferiblemente, si la administración no es simultánea, los compuestos se administran de manera próxima en el tiempo. Además, no importa si los compuestos se administran en la misma forma de dosificación, por ejemplo, un compuesto puede administrarse por vía tópica y otro compuesto puede administrarse por vía oral.

Típicamente, en el tratamiento de cáncer de la presente invención puede coadministrarse cualquier agente antineoplásico que tenga actividad contra un tumor susceptible que se esté tratando. Pueden encontrarse ejemplos de tales agentes en Cancer Principles and Practice of Oncology por V.T. Devita y S. Hellman (editors), 6ª edición (15 de febrero de 2001), Lippincott Williams & Wilkins Publishers. Una persona con experiencia normal en la técnica podría determinar las combinaciones de agentes que serían útiles basándose en las características particulares de los fármacos y el cáncer implicado. Los agentes antineoplásicos típicos útiles en la presente invención incluyen, pero sin limitación, agentes anti-microtubulares tales como diterpenoides y alcaloides de la vinca; complejos de coordinación de platino; agentes alquilantes tales como mostazas nitrogenadas, oxazafosforinas, alquilsulfonatos, nitrosoureas y triazenos; agentes antibióticos tales como antraciclinas, actinomicinas y bleomicinas; inhibidores de topoisomerasa II tales como epipodofilotoxinas; antimetabolitos tales como análogos de purina y pirimidina y compuestos anti-folato; inhibidores de topoisomerasa I tales como camptotecinas; hormonas y análogos hormonales; inhibidores de la ruta de transducción de señales; inhibidores de la angiogénesis de tirosina quinasas no asociadas a receptores; agentes inmunoterapéuticos; agentes proapoptóticos; e inhibidores de la señalización del ciclo celular.

Son ejemplos de un ingrediente o ingredientes activos adicionales (agente anti-neoplásico) para uso en combinación o co-administración con los compuestos que inhiben AKT de la presente invención agentes quimioterapéuticos.

Los agentes anti-microtubulares o antimitóticos son agentes con especificidad de fase activos contra los microtúbulos de las células tumorales durante la fase M o de mitosis del ciclo celular. Los ejemplos de agentes anti-microtubulares incluyen, pero sin limitación, diterpenoides y alcaloides de la vinca.

Los diterpenoides, que proceden de fuentes naturales, son agentes contra el cáncer con especificidad de fase que actúan en las fases G_2/M del ciclo celular. Se cree que los diterpenoides estabilizan la subunidad β-tubulina de los microtúbulos, por medio de su unión a esta proteína. Entonces, parece ser que se inhibe el desensamblaje de la proteína, deteniéndose la mitosis y produciéndose posteriormente la muerte celular. Los ejemplos de diterpenoides incluyen, pero sin limitación, paclitaxel y su análogo docetaxel.

El paclitaxel, 13-éster de 4,10-diacetato 2-benzoato de 5β,20-epoxi-1,2α,4,7β,10β,13α-hexa-hidroxitax-11-en-9-ona con (2R,3S)-N-benzoil-3-fenilisoserina; es un producto de diterpeno natural aislado del tejo del Pacífico *Taxus brevifolia* y está disponible en el mercado como una solución inyectable TAXOL®. Es un miembro de la familia de terpenos que recibe el nombre de taxanos. Se aisló por primera vez en 1971 por Wani et al. J. Am. Chem, Soc., 93:2325, 1971), que caracterizó su estructura por métodos químicos y de cristalografía de rayos X. Un mecanismo para su actividad se refiere a la capacidad del paclitaxel para unirse a la tubulina, inhibiéndose de esta manera el crecimiento de células cancerosas. Schiff et al., Proc. Natl, Acad, Sci. USA, 77:1561-1565 (1980); Schiff et al., Nature, 277:665-667 (1979); Kumar, J. Biol, Chem, 256: 10435-10441 (1981). Como revisión de la síntesis y actividad anticancerosa de algunos derivados de paclitaxel véase: D. G. I. Kingston *et al.*, Studies in Organic Chemistry vol. 26, titulado "New trends in Natural Products Chemistry 1986", Attaur-Rahman, P.W. Le Quesne, Eds. (Elsevier, Amsterdam, 1986) páginas 219-235.

El paclitaxel se ha aprobado para uso clínico en el tratamiento de cáncer de ovario refractario en los Estados Unidos (Markman et al., Yale Journal of Biology and Medicine, 64:583, 1991; McGuire et al., Ann. Intem, Med., 111:273,1989) y para el tratamiento de cáncer de mama (Holmes et al., J. Nat. Cancer Inst., 83:1797,1991). Es un candidato potencial para el tratamiento de neoplasmas en la piel (Einzig et. al., Proc. Am. Soc. Clin. Oncol., 20:46) y carcinomas de cabeza y cuello (Forastire et. al., Sem. Oncol., 20:56, 1990). El compuesto también muestra potencial para el tratamiento de la enfermedad renal poliquística (Woo et. al., Nature, 368:750, 1994), cáncer de pulmón y malaria. El tratamiento de pacientes con paclitaxel reprime la médula ósea (múltiples linajes celulares, Ignoff, R.J. et. al, Cancer Chemotherapy Pocket Guide, 1998) de manera relacionada con la duración de la dosificación por encima de una concentración límite (50 nM) (Kearns, C.M. et. al., Seminars en Oncology, 3(6) p.16-23, 1995).

El docetaxel, 13-éster de N-*terc*-butil éster de (2R,3S)-N-carboxi-3-fenilisoserina con 4-acetato 2-benzoato de 5β-20-epoxi-1,2α,4,7β,10β,13α-hexahidroxitax-11-en-9-ona, trihidrato; está disponible en el mercado como una solución inyectable denominada TAXOTERE®. El docetaxel está indicado para el tratamiento de cáncer de mama. El docetaxel es un derivado semisintético de paclitaxel *q.v.*, preparado usando un precursor natural, 10-desacetil-bacatina III,

extraído a partir de las acículas del tejo europeo. La toxicidad limitante de la dosis de docetaxel es la neutropenia.

Los alcaloides de la vinca son agentes antineoplásicos con especificidad de fase derivados de la planta vincapervinca. Los alcaloides de la vinca actúan en la fase M (mitosis) del ciclo celular por medio de su unión específica a la tubulina. Por consiguiente, la molécula de tubulina unida no puede polimerizar para formar microtúbulos. Se cree que la mitosis se detiene en la metafase produciéndose posteriormente la muerte celular. Los ejemplos de alcaloides de la vinca incluyen, pero sin limitación, vinblastina, vincristina y vinorelbina.

La vinblastina, sulfato de vincaleucoblastina, está disponible en el mercado con el nombre VELBAN®, como una solución inyectable. Aunque tiene una posible indicación como una terapia de segunda línea de diversos tumores sólidos, principalmente está indicada en el tratamiento de cáncer de testículos y diversos linfomas incluyendo la enfermedad de Hodgkin; y linfomas linfocíticos e histiocíticos. La mielosupresión es el efecto secundario limitante de la dosis de la vinblastina.

La vincristina, vincaleucoblastina, 22-oxo-, sulfato, está disponible en el mercado con el nombre ONCOVIN® como una solución inyectable. La vincristina está indicada para el tratamiento de leucemias agudas y también ha encontrado utilidad en regímenes de tratamiento para linfomas malignos de Hodgkin y no Hodgkin. Los efectos secundarios más comunes de la vincristina son alopecia y efectos neurológicos y, en una menor medida, se producen efectos mielosupresores y mucositis gastrointestinal.

La vinorelbina, 3',4'-dideshidro-4'-desoxi-C'-norvincaleucoblastina [R-(R*,R*)-2,3-dihidroxibutanodioato (1:2)(sal)], disponible en el mercado como una solución inyectable de tartrato de vinorelbina (NAVELBINE®), es un alcaloide de la vinca semisintético. La vinorelbina está indicada, como un solo agente o en combinación con otros agentes quimioterapéuticos, tales como cisplatino, en el tratamiento de diversos tumores sólidos, particularmente cánceres no microcíticos de pulmón, cáncer de mama avanzado y cáncer de próstata refractario a hormonas. La mielosupresión es el efecto secundario limitante de la dosis más común de la vinorelbina.

Los complejos de coordinación de platino son agentes contra el cáncer no específicos de fase que interaccionan con el ADN. Los complejos de platino entran

en las células tumorales, experimentan hidratación y forman entrecruzamientos intra- e intercatenarios con el DNA causando efectos biológicos adversos en el tumor. Los ejemplos de complejos de coordinación de platino incluyen, pero sin limitación, cisplatino y carboplatino.

El cisplatino, cis-diaminadicloroplatino, está disponible en el mercado con el nombre PLATINOL® como una solución inyectable. El cisplatino está indicado principalmente en el tratamiento de cáncer metastásico testicular y de ovario y en cáncer de vejiga avanzado. Los efectos secundarios limitantes de la dosis principales del cisplatino son nefrotoxicidad, que puede controlarse por hidratación y diuresis, y ototoxicidad.

El carboplatino, diamina [1,1-ciclobutano-dicarboxilato(2-)-O,O'] de platino, está disponible en el mercado con el nombre PARAPLATIN® como una solución inyectable. El carboplatino está indicado principalmente en el tratamiento de primera y segunda línea del carcinoma de ovario avanzado. La toxicidad limitante de la dosis del carboplatino es la represión de la médula ósea.

Los agentes alquilantes son agentes contra el cáncer sin especificidad de fase y son electrófilos fuertes. Típicamente, los agentes alquilantes forman enlaces covalentes, por alquilación, con el DNA a través de restos nucleófilos de la molécula de ADN tales como grupos fosfato, amino, sulfhidrilo, hidroxilo, carboxilo e imidazol. Esta alquilación altera la función del ácido nucleico produciendo muerte celular. Los ejemplos de agentes alquilantes incluyen, pero sin limitación, mostazas nitrogenadas tales como ciclofosfamida, melfalan y clorambucilo; alquil sulfonatos tales como busulfan; nitrosoureas tales como carmustina; y triazenos tales como dacarbazina.

La ciclofosfamida, el 2-óxido de 2-[bis(2-cloroetil)amino]tetrahidro-2H-1,3,2-oxazafosforina monohidrato, está disponible en el mercado como una solución inyectable o como comprimidos con el nombre CYTOXAN®. La ciclofosfamida está indicada como un solo agente o en combinación con otros agentes quimioterapéuticos, en el tratamiento de linfomas malignos, mieloma múltiple y leucemias. Los efectos secundarios limitantes de la dosis más comunes de la ciclofosfamida son alopecia, náuseas, vómitos y leucopenia.

El malfalan, 4-[bis(2-cloroetil)amino]-L-fenilalanina, está disponible en el mercado como una solución inyectable o comprimidos con el nombre ALKERAN®. El melfalan está indicado para el tratamiento paliativo del mieloma múltiple y el

carcinoma epitelial no reseccionable del ovario. La represión de la médula ósea es el efecto secundario limitante de la dosis más común del melfalan.

El clorambucilo, ácido 4-[bis(2-cloroetil)amino]bencenobutanoico, está disponible en el mercado como comprimidos con el nombre LEUKERAN®. El clorambucilo está indicado para el tratamiento paliativo de la leucemia linfática crónica, y de linfomas malignos tales como linfosarcoma, linfoma folicular gigante y enfermedad de Hodgkin. La represión de la médula ósea es el efecto secundario limitante de la dosis más común del clorambucilo.

El busulfan, dimetanosulfonato de 1,4-butanodiol, está disponible en el mercado como comprimidos con el nombre MYLERAN®. El busulfan está indicado para el tratamiento paliativo de la leucemia mielógena crónica. La represión de la médula ósea es el efecto secundario limitante de la dosis más común del busulfan.

La carmustina, 1,3-[bis(2-cloroetil)-1-nitrosourea, está disponible en el mercado como viales individuales de material liofilizado con el nombre BiCNU®. La carmustina está indicada para el tratamiento paliativo como un solo agente o en combinación con otros agentes para tumores cerebrales, mieloma múltiple, enfermedad de Hodgkin y linfomas no Hodgkin. La mielosupresión retardada es el efecto secundario limitante de la dosis más común de la carmustina.

La dacarbazina, 5-(3,3-dimetil-1-triazeno)-imidazol-4-carboxamida, está disponible en el mercado como viales individuales de material con el nombre DTIC-Dome®. La dacarbazina está indicada para el tratamiento del melanoma maligno metastásico y en combinación con otros agentes para el tratamiento de segunda línea de la enfermedad de Hodgkin. Las náuseas, vómitos y anorexia son los efectos secundarios limitantes de la dosis más comunes de la dacarbazina.

Los antineoplásicos antibióticos son agentes sin especificidad de fase, que se unen o intercalan con el ADN. Típicamente, esta acción produce complejos de ADN estables o roturas de cadena, que alteran la función habitual de los ácidos nucleicos ocasionando muerte celular. Los ejemplos de agentes antineoplásicos antibióticos incluyen, pero sin limitación, actinomicinas, tales como dactinomicina, antraciclinas tales como daunorubicina y doxorubicina; y bleomicinas.

La dactinomicina, también conocida como Actinomicina D, está disponible en el mercado en una formulación inyectable con el nombre COSMEGEN®. La dactinomicina está indicada para el tratamiento n está indicada para el tratamiento

del tumor de Wilm y el rabdomiosarcoma. Las náuseas, vómitos y anorexia son los efectos secundarios limitantes de la dosis más comunes de la dactinomicina.

La daunorubicina, hidrocloruro de (8S-cis)-8-acetil-10-[(3-amino-2,3,6-trideoxi-α-L-lixo-hexopiranosil)oxi]-7,8,9,10-tetrahidro-6,8,11-trihidroxi-1-metoxi-5,12 naftacenodiona, está disponible en el mercado como una formulación inyectable liposomal con el nombre DAUNOXOME® o como un inyectable con el nombre CERUBIDINE®. La daunorubicina está indicada para la inducción de remisión en el tratamiento de la leucemia no linfocítica aguda y el sarcoma de Kaposi asociado a VIH avanzado. La mielosupresión es el efecto secundario limitante de la dosis más común de la daunorubicina.

La doxorubicina, hidrocloruro de (8S, 10S)-10-[(3-amino-2,3,6-trideoxi-α-L-lixo-hexopiranosil)oxi]-8-glicoloil, 7,8,9,10-tetrahidro-6,8,11-trihidroxi-1-metoxi-5,12 naftacenodiona, está disponible en el mercado como una formulación inyectable con el nombre RUBEX® o ADRIAMYCIN RDF®. La doxorubicina está indicada principalmente para el tratamiento de la leucemia linfoblástica aguda y la leucemia mieloblástica aguda, pero también es un componente útil en el tratamiento de algunos tumores sólidos y linfomas. La mielosupresión es el efecto secundario limitante de la dosis más común de la doxorubicina.

La bleomicina, una mezcla de antibióticos glicopeptídicos citotóxicos aislados a partir de una cepa de *Streptomyces verticillus*, está disponible en el mercado como BLENOXANE®. La bleomicina está indicada como un tratamiento paliativo, como un solo agente o en combinación con otros agentes, del carcinoma de células escamosas, linfomas y carcinomas testiculares. Las toxicidades pulmonar y cutánea son los efectos secundarios limitantes de la dosis más comunes de la bleomicina.

Los inhibidores de la topoisomerasa II incluyen, pero sin limitación, epipodofilotoxinas.

Las epipodofilotoxinas son agentes antineoplásicos con especificidad de fase derivados de la planta mandrágora. Las epipodofilotoxinas típicamente afectan a las células en las fases S y G_2 del ciclo celular formando un complejo ternario con la topoisomerasa II y el ADN causando roturas en las cadenas de ADN. Las roturas de las cadenas se acumulan y posteriormente se produce muerte celular. Los ejemplos de epipodofilotoxinas incluyen, pero sin limitación, etopósido y tenipósido.

El etopósido, 4'-desmetil-epipodofilotoxina 9[4,6-0-(R)-etilideno-β-D-glucopiranósido], está disponible en el mercado como una solución inyectable o cápsulas con el nombre VePESID® y se conoce comúnmente como VP-16. El etopósido está indicado como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento de cáncer testicular y de cánceres no microcíticos de pulmón. La mielosupresión es el efecto secundario más común del etopósido. La incidencia de leucopenia tiende a ser más severa que la trombocitopenia.

El tenipósido, 4'-desmetil-epipodofilotoxina 9[4,6-0-(R)-tenilideno-β-D-glucopiranósido], está disponible en el mercado como una solución inyectable con el nombre VUMON® y comúnmente se conoce como VM-26. El tenipósido está indicado como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda en niños. La mielosupresión es el efecto secundario limitante de la dosis más común del tenipósido. El tenipósido puede inducir tanto leucopenia como trombocitopenia.

Los agentes neoplásicos antimetabolitos son agentes antineoplásicos con especificidad de fase que actúan en la fase S (síntesis de ADN) del ciclo celular por medio de la inhibición de la síntesis de ADN o por medio de la inhibición de la síntesis de bases de purina o pirimidina, limitando de esta manera la síntesis de ADN. Por consiguiente, no continúa la fase S y se produce la muerte celular. Los ejemplos de agentes antineoplásicos antimetabolito incluyen, pero sin limitación, fluorouracilo, metotrexato, citarabina, mecarptopurina, tioguanina y gemcitabina.

El 5-fluorouracilo, 5-fluoro-2,4-(1H,3H) pirimidinadiona, está disponible en el mercado como fluorouracilo. La administración de 5-fluorouracilo conduce a la inhibición de la síntesis de timidilato y también se incorpora tanto en el ARN como en el ADN. El resultado típicamente es la muerte celular. El 5-fluorouracilo está indicado como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento de carcinomas de mama, colon, recto, estómago y páncreas. La mielosupresión y la mucositis son efectos secundarios limitantes de la dosis del 5-fluorouracilo. Otros análogos de fluoropirimidina incluyen 5-fluoro desoxiuridina (floxuridina) y 5-fluorodesoxiuridina monofosfato.

La citarabina, 4-amino-1-β-D-arabinofuranosil-2(1H)-pirimidinona, está disponible en el mercado con el nombre CYTOSAR-U® y se conoce comúnmente como Ara-C. Se cree que la citarabina presenta especificidad de fase celular en la

fase S inhibiendo el alargamiento de la cadena de ADN por incorporación terminal de citarabina en la cadena de ADN en crecimiento. La citarabina está indicada como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda. Otros análogos de citidina incluyen 5-azacitidina y 2',2'-difluorodesoxicitidina (gemcitabina). La citarabina induce leucopenia, trombocitopenia y mucositis.

La mercaptopurina, 1,7-dihidro-6H-purine-6-tiona monohidrato, está disponible en el mercado como PURINETHOL®. La mercaptopurina presenta especificidad de fase celular en la fase S por medio de la inhibición de la síntesis de ADN por un mecanismo no especificado hasta ahora. La mercaptopurina está indicada como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda. La mielosupresión y la mucositis gastrointestinal son efectos secundarios esperados de la mercaptopurina a altas dosis. Un análogo de mercaptopurina útil es azatioprina.

La tioguanina, 2-amino-1,7-dihidro-6H-purine-6-tiona, está disponible en el mercado como TABLOID®. La tioguanina presenta especificidad de fase celular en la fase S por medio de la inhibición de la síntesis de ADN por un mecanismo no especificado hasta ahora. La tioguanina está indicada como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento de la leucemia aguda. La mielosupresión, incluyendo leucopenia, trombocitopenia y anemia, es el efecto secundario limitante de la dosis más común de la administración de tioguanina. Sin embargo, aparecen efectos secundarios gastrointestinales y pueden ser limitantes de la dosis. Otros análogos de purina incluyen pentostatina, eritrohidroxinoniladenina, fosfato de fludarabina y cladribina.

La gemcitabina, monohidrocloruro de 2'-desoxi-2',2'-difluorocitidina (isómero β), está disponible en el mercado como GEMZAR®. La gemcitabina presenta especificidad de fase celular en la fase S por medio del bloqueo de la progresión de las células a lo largo del límite G1/S. La gemcitabina está indicada en combinación con cisplatino en el tratamiento de cáncer pulmonar no microcítico localmente avanzado e individualmente en el tratamiento de cáncer pancreático localmente avanzado. La mielosupresión, incluyendo leucopenia, trombocitopenia y anemia, es el efecto secundario limitante de la dosis más común de la administración de gemcitabina.

El metotrexato, ácido N-[4[[(2,4-diamino-6-pteridinil)metil]metilamino]benzoil]-L-glutámico, está disponible en el mercado como metotrexato sódico. El metotrexato presenta efectos de fase celular específicamente en la fase S por medio de la inhibición de la síntesis, reparación y/o replicación de ADN a través de la inhibición de la ácido dihidrofólico reductasa que se requiere para la síntesis de nucleótidos de purina y timidilato. El metotrexato está indicado como un solo agente o en combinación con otros agentes quimioterapéuticos en el tratamiento del coriocarcinoma, leucemia meníngea, linfoma no Hodgkin y carcinomas de mama, cabeza, cuello, ovario y vejiga. La mielosupresión (leucopenia, trombocitopenia y anemia) y la mucositis son efectos secundarios esperados de la administración de metotrexato.

Las camptotecinas, incluyendo la camptotecina y derivados de camptotecina, están disponibles o están en desarrollo como inhibidores de la Topoisomerasa I. Se cree que la actividad citotóxica de las camptotecinas está relacionada con su actividad inhibidora de la Topoisomerasa I. Los ejemplos de camptotecinas incluyen, pero sin limitación, irinotecan, topotecan y las diversas formas ópticas de 7-(4-metilpiperazino-metileno)-10,11-etilenodioxi-20-camptotecina descritas más adelante.

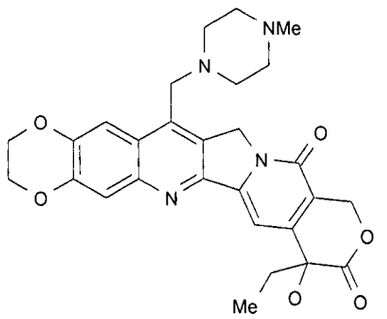
El irinotecan HCl, hidrocloruro de (4S)-4,11-dietil-4-hidroxi-9-[(4-piperidinopiperidino)carboniloxi]-1H-pirano[3',4',6,7]indolizino[1,2-b]quinolina-3,14(4H,12H)-diona, está disponible en el mercado como la solución inyectable CAMPTOSAR®.

El irinotecan es un derivado de camptotecina que se une, junto con su metabolito activo SN-38, al complejo de topoisomerasa I – ADN. Se cree que la citotoxicidad se produce como resultado de roturas irreparables en la doble cadena producidas por la interacción de la topoisomerasa I: ADN: irinotecan o el complejo ternario SN-38 con enzimas de replicación. El irinotecan está indicado para el tratamiento de cáncer metastásico de colon o recto. Los efectos secundarios limitantes de la dosis del irinotecan HCl son mielosupresión, incluyendo neutropenia, y efectos GI, incluyendo diarrea.

El topotecan HCl, monohidrocloruro de (S)-10-[(dimetilamino)metil]-4-etil-4,9-dihidroxi-1H-pirano[3',4',6,7]indolizino[1,2-b]quinolina-3,14-(4H,12H)-diona, está disponible en el mercado como la solución inyectable HYCAMTIN®. El topotecan es un derivado de la camptotecina que se une al complejo de topoisomerasa I –

ADN e impide el religamiento de roturas de cadenas sencillas producidas por la Topoisomerasa I en respuesta a una tensión de torsión de la molécula de ADN. El topotecan está indicado para el tratamiento de segunda línea de carcinoma metastásico del ovario y cáncer microcítico de pulmón. El efecto secundario limitante de la dosis del topotecan HCl es mielosupresión, principalmente neutropenia.

También es de interés el derivado de camptotecina de la fórmula A mostrada a continuación, actualmente en desarrollo, incluyendo la mezcla racémica (R,S) así como los enantiómeros R y S:



A

conocidos por el nombre químico "7-(4-metilpiperazino-metileno)-10,11-etilenodioxi-20(R,S)-camptotecina (mezcla racémica) o "7-(4-metilpiperazino-metileno)-10,11-etilenodioxi-20(R)-camptotecina (enantiómero R) o "7-(4-metilpiperazino-metileno)-10,11-etilenodioxi-20(S)-camptotecina (enantiómero S). Estos compuestos, así como los compuestos relacionados, se describen, incluyendo métodos para su fabricación, en las Patentes de Estados Unidos Nº 6.063.923; 5.342.947; 5.559.235; 5.491.237 y en la Solicitud de Patente de Estados Unidos Nº 08/977.217 presentada el 24 de noviembre de 1997.

Ciertas hormonas y análogos hormonales son compuestos útiles para tratar cánceres, en los que existe una relación entre las hormonas y el crecimiento y/o ausencia de crecimiento del cáncer. Los ejemplos de hormonas y análogos de hormonas útiles en el tratamiento de cánceres incluyen, pero sin limitación, adrenocorticosteroides tales como prednisona y prednisolona que son útiles en el tratamiento de linfomas malignos y la leucemia aguda en niños; aminoglutetimida y otros inhibidores de aromatasa tales como anastrozol, letrazol, vorazol y exemestano útiles en el tratamiento del carcinoma adrenocortical y el carcinoma de mama dependiente de hormonas que contiene receptores de estrógenos; progestinas tales como acetato de megestrol útiles en el tratamiento de cáncer de

mama dependiente de hormonas y carcinoma endometrial; estrógenos, andrógenos y anti-andrógenos tales como flutamida, nilutamida, bicalutamida, acetato de ciproterona y 5α-reductasas tales como finasteride y dutasteride, útiles en el tratamiento del carcinoma prostático y la hipertrofia prostática benigna; anti-estrógenos tales como tamoxifeno, toremifeno, raloxifeno, droloxifeno, yodoxifeno, así como moduladores selectivos de receptores de estrógenos (SERMS) tales como los descritos en las Patentes de Estados Unidos Nº 5,681,835, 5,877,219 y 6,207,716, útiles en el tratamiento de carcinomas de mama dependientes de hormonas y otros cánceres susceptibles; y hormona de liberación de gonadotropina (GnRH) y análogos de la misma que estimulan la liberación de hormona luteinizante (LH) y/o de hormona estimuladora del folículo (FSH) para el tratamiento del carcinoma de próstata, por ejemplo, agonistas y antagonistas de LHRH tales como acetato de goserelina y leuprolida.

Los inhibidores de la ruta de transducción de señales son los inhibidores que bloquean o inhiben un proceso químico que provoca un cambio intracelular. Como se usa en este documento, este cambio es la proliferación o diferenciación celular. Los inhibidores de la transducción de señales útiles en la presente invención incluyen inhibidores de tirosina quinasas asociadas a receptores, de tirosina quinasas no asociadas a receptores, bloqueantes del dominio SH2/SH3, serina/treonina quinasas, fosfatidil inositol-3 quinasas, señalización de mio-inositol y oncogenes Ras.

Varias proteína tirosina quinasas catalizan la fosforilación de restos de tirosilo específicos en diversas proteínas implicadas en la regulación del crecimiento celular. Estas proteína tirosina quinasas pueden clasificarse en sentido amplio como quinasas asociadas a receptores y no asociadas a receptores.

Las tirosina quinasas asociadas a receptores son proteínas transmembrana que tienen un dominio de unión al ligando extracelular, un dominio transmembrana y un dominio tirosina quinasa. Las tirosina quinasas asociadas a receptores están implicadas en la regulación del crecimiento celular y generalmente se denominan receptores de factores de crecimiento. Se ha demostrado que una activación inapropiada o incontrolada de muchas de estas quinasas, es decir, una actividad aberrante de un receptor de factor de crecimiento quinasa, por ejemplo, por sobre-expresión o mutación, tiene como resultado un crecimiento celular incontrolado. Por consiguiente, la actividad aberrante de estas quinasas se ha asociado con el crecimiento maligno de tejidos. Por consiguiente, los inhibidores de estas quinasas

podrían proporcionar métodos de tratamiento de cánceres. Los receptores de factores de crecimiento incluyen, por ejemplo, el receptor del factor de crecimiento epidérmico (EGFr), el receptor del factor de crecimiento derivado de plaquetas (PDGFr), erbB2, erbB4, el receptor del factor de crecimiento derivado del endotelio vascular (VEGFr), tirosina quinasa con dominios de tipo inmunoglobulina y dominios de homología al factor de crecimiento epidérmico (TIE-2), receptor del factor de crecimiento semejante a insulina–I (IGFI), factor estimulador de colonias de macrófagos (cfms), BTK, ckit, cmet, receptores del factor de crecimiento de fibroblastos (FGF), receptores Trk (TrkA, TrkB, y TrkC), receptores de efrina (eph) y el protooncogen RET. Varios inhibidores de receptores de crecimiento están en desarrollo e incluyen antagonistas de ligandos, anticuerpos, inhibidores de tirosina quinasa y oligonucleótidos antisentido. Se describen receptores del factor de crecimiento y agentes que inhiben la función del receptor del factor de crecimiento, por ejemplo, en Kath, John C., Exp. Opin. Ther. Patents (2000) 10(6):803-818; Shawver et al DDT Vol 2, No. 2 Febrero de 1997; y Lofts, F. J. et al, "Growth factor receptors as targets", New Molecular Targets for Cancer Chemotherapy, ed. Workman, Paul y Kerr, David, CRC press 1994, London.

Las tirosina quinasas que no son quinasas asociadas a receptores de factores de crecimiento se denominan tirosina quinasas no asociadas a receptores. Las tirosina quinasas no asociadas a receptores para uso en la presente invención, que son dianas o dianas potenciales de fármacos anticancerosos, incluyen cSrc, Lck, Fyn, Yes, Jak, cAbl, FAK (quinasa de adhesión focal), tirosina quinasa Brutons y Bcr-Abl. Se describen estas quinasas no asociadas a receptores y agentes que inhiben la función de tirosinas quinasas no asociadas receptores en Sinh, S. y Corey, S.J., (1999) Journal of Hematotherapy and Stem Cell Research 8 (5): 465 – 80; y Bolen, J.B., Brugge, J.S., (1997) Annual review of Immunology. 15: 371-404.

Los bloqueantes del dominio SH2/SH3 son agentes que impiden la unión del dominio SH2 o SH3 en una diversidad de enzimas o proteínas adaptadoras incluyendo la subunidad p85 de PI3-K, quinasas de la familia Src, moléculas adaptadoras (Shc, Crk, Nck, Grb2) y Ras-GAP. Se describen dominios SH2/SH3 como dianas para fármacos contra el cáncer en Smithgall, T.E. (1995), Journal of Pharmacological and Toxicological Methods. 34(3) 125-32.

Inhibidores de Serina/Treonina Quinasas incluyendo bloqueantes de la cascada de la quinasa MAP que incluyen bloqueantes de quinasas Raf (rafk), Quinasa Regulada por Mitógenos o por señales Extracelulares (MEK) y Quinasas

Reguladas por señales Extracelulares (ERK); y bloqueantes de miembros de la familia de la proteína quinasa C incluyendo bloqueantes de PKC (alfa, beta, gamma, épsilon, mu, lambda, iota, zeta). Quinasas de la familia IkB (IKKa, IKKb), quinasas de la familia PKB, miembros de la familia de la quinasa akt, y quinasas asociadas a receptores de TGF beta. Estas Serina/Treonina quinasas y sus inhibidores se describen en Yamamoto, T., Taya, S., Kaibuchi, K., (1999), Journal of Biochemistry. 126 (5) 799-803; Brodt, P, Samani, A., y Navab, R. (2000), Biochemical Pharmacology, 60, 1101-1107; Massague, J., Weis-Garcia, F. (1996) Cancer Surveys. 27:41-64; Philip, P.A., y Harris, A.L. (1995), Cancer Treatment and Research. 78: 3-27, Lackey, K. et al Bioorganic and Medicinal Chemistry Letters, (10), 2000, 223-226; Patente de Estados Unidos Nº 6,268,391; y Martinez-Iacaci, L., et al, Int. J. Cancer (2000), 88(1), 44-52.

También pueden ser útiles en la presente invención inhibidores de los miembros de la familia de la fosfatidil inositol-3 quinasa, incluyendo los bloqueantes de la PI3-quinasa, ATM, DNA-PK y Ku. Estas quinasas se describen en Abraham, R.T. (1996), Current Opinion in Immunology. 8 (3) 412-8; Canman, C.E., Lim, D.S. (1998), Oncogene 17 (25) 3301-3308; Jackson, S.P. (1997), International Journal of Biochemistry and Cell Biology. 29 (7):935-8; y Zhong, H. et al, Cancer res, (2000) 60(6), 1541-1545.

También son de interés en la presente invención inhibidores de la señalización de mioinositol tales como bloqueantes de la fosfolipasa C y análogos de mioinositol. Estos inhibidores de señales se describen en Powis, G., y Kozikowski A., (1994) New Molecular Targets for Cancer Chemotherapy ed., Paul Workman y David Kerr, CRC press 1994, London.

Otro grupo de inhibidores de la ruta de transducción de señales son inhibidores del oncogen Ras. Estos inhibidores incluyen inhibidores de la farnesil transferasa, geranil-geranil transferasa, y proteasas CAAX, así como oligonucleótidos antisentido, ribozimas e inmunoterapia. Se ha demostrado que estos inhibidores bloquean la activación de ras en células que contienen el mutante ras de tipo silvestre, actuando de esta manera como agentes contra la proliferación. Se describe la inhibición del oncogen Ras en Scharovsky, O.G., Rozados, V.R., Gervasoni, S.I. Matar, P. (2000), Journal of Biomedical Science. 7(4) 292-8; Ashby, M.N. (1998), Current Opinion in Lipidology. 9 (2) 99 – 102; y BioChim. Biophys. Acta, (19899) 1423(3):19-30,

Como se ha mencionado anteriormente, también pueden servir como inhibidores de la transducción de señales anticuerpos antagonistas de la unión de ligandos de quinasas asociadas a receptores. Este grupo de inhibidores de la ruta de transducción de señales incluye el uso de anticuerpos humanizados contra el dominio de unión al ligando extracelular de tirosina quinasas asociadas a receptores. Por ejemplo, el anticuerpo específico Imclone C225 EGFR (véase Green, M.C. et al, Monoclonal Antibody Therapy for Solid Tumors, Cancer Treat. Rev., (2000), 26(4), 269-286); el anticuerpo Herceptin® erbB2 (véase Tyrosine Kinase Signalling in Breast cancer:erbB Family Receptor Tyrosine Kinases, Breast Cancer Res., 2000, 2(3), 176-183); y el anticuerpo específico 2CB VEGFR2 (véase Brekken, R.A. et al, Selective Inhibition of VEGFR2 Activity by a monoclonal Anti-VEGF antibody blocks tumor growth in mice, Cancer Res. (2000) 60, 5117-5124).

En la presente invención también pueden ser útiles inhibidores de la angiogénesis que no son quinasas asociadas a receptores. Anteriormente se han descrito los inhibidores de la angiogénsis relacionados VEGFR y TIE2 en relación con inhibidores de la transducción de señales (los dos receptores son tirosina quinasas asociadas a receptores). La angiogénesis en general está asociada con la señalización erbB2/EGFR, ya que se ha demostrado que los inhibidores de erbB2 y EGFR inhiben la angiogénesis, principalmente la expresión de VEGF. Por consiguiente, pueden usarse inhibidores de tirosina quinasas no asociadas con receptores en combinación con los compuestos de la presente invención. Por ejemplo, también pueden resultar útiles en combinación con los compuestos descritos anticuerpos anti-VEGF que no reconocen a VEGFR (la tirosina quinasa asociada al receptor), pero se unen al ligando; inhibidores de integrina de molécula pequeña (alfa$_v$ beta$_3$) que inhibirán la angiogénesis; endostatina y angiostatina (no-RTK). (Véase Bruns CJ et al (2000), Cancer Res., 60: 2926-2935; Schreiber AB, Winkler ME, y Derynck R. (1986), Science, 232: 1250-1253; Yen L et al. (2000), Oncogene 19: 3460-3469).

También pueden ser útiles en combinación con los compuestos de fórmula (I) agentes usados en regímenes inmunoterapéuticos. Existen varias estrategias inmunológicas para generar una respuesta inmune. Estas estrategias generalmente están en el campo de las vacunaciones tumorales. La eficacia de las estrategias inmunológicas puede mejorarse en gran medida por medio de la inhibición combinada de rutas de señalización usando un inhibidor de pequeña molécula. Se encuentra una discusión del procedimiento inmunológico/vacuna tumoral contra

erbB2/EGFR en Reilly RT et al. (2000), Cancer Res. 60: 3569-3576; y Chen Y, Hu D, Eling DJ, Robbins J, y Kipps TJ. (1998), Cancer Res. 58: 1965-1971.

En la combinación de la presente invención también pueden usarse agentes usados en regímenes proapoptóticos (por ejemplo, oligonucleótidos antisentido bcl-2). Ciertos miembros de la familia de proteínas Bcl-2 bloquean la apoptosis. Por lo tanto, la regulación positiva de bcl-2 se ha asociado con quimiorresistencia. Ciertos estudios han demostrado que el factor de crecimiento epidérmico (EGF) estimula a miembros anti-apoptóticos de la familia bcl-2 (es decir, mcl-1). Por lo tanto, ciertas estrategias diseñadas para regular negativamente la expresión de bcl-2 en tumores han demostrado tener un efecto clínico beneficioso y ahora están en ensayos de Fase II/III, particularmente el oligonucleótido antisentido G3139 bcl-2 de Genta. Se describen estas estrategias proapoptóticas que usan la estrategia de oligonucleótidos antisentido para bcl-2 en Water JS et al. (2000), J. Clin. Oncol. 18: 1812-1823; y Kitada S et al. (1994), Antisense Res. Dev. 4: 71-79.

Los inhibidores de la señalización del ciclo celular inhiben moléculas implicadas en el control del ciclo celular. Una familia de proteína quinasas denominadas quinasas dependientes de ciclina (CDK) y su interacción con una familia de proteínas denominadas ciclinas controla la progresión a través del ciclo de células eucariotas. La activación e inactivación coordinadas de diferentes complejos de ciclina/CDK es necesaria para la progresión normal a través del ciclo celular. Varios inhibidores de la señalización del ciclo celular están en desarrollo. Por ejemplo, se describen ejemplos de quinasas dependientes de ciclina, incluyendo CDK2, CDK4 y CDK6 e inhibidores para los mismos, por ejemplo, en Rosania et al, Exp. Opin. Ther. Patents (2000) 10(2):215-230.

En una realización, el método de tratamiento de cáncer de la invención reivindicada incluye la coadministración de un compuesto de Fórmula (I) y/o una sal farmacéuticamente aceptable del mismo y al menos un agente antineoplásico, tal como uno seleccionado entre el grupo consistente en agentes anti-microtúbulos, complejos de coordinación con platino, agentes alquilantes, agentes antibióticos, inhibidores de la topoisomerasa II, antimetabolitos, inhibidores de la topoisomerasa I, hormonas y análogos hormonales, inhibidores de rutas de transducción de señales, inhibidores de la angiogénesis que no son tirosina quinasas asociadas a receptores, agentes inmunoterapéuticos, agentes proapoptóticos e inhibidores de la señalización del ciclo celular.

Como los compuestos farmacéuticamente activos de la presente invención son activos como inhibidores de AKT, presentan utilidad terapéutica en el tratamiento de cánceres y de artritis.

Convenientemente, la presente invencion se refiere a un método para tratar o reducir la gravedad de un cáncer seleccionado entre: cerebral (gliomas), glioblastomas, síndrome de Bannayan-Zonana, enfermedad de Cowden, enfermedad de Lhermitte-Duclos, de mama, cáncer de mama inflamatorio, tumor de Wilm, sarcoma de Ewing, Rabdomiosarcoma, ependimoma, meduloblastoma, de colon, de cabeza y cuello, de riñón, de pulmón, de hígado, melanoma, de ovario, pancreático, de próstata, sarcoma, osteosarcoma, tumor óseo de células gigantes, tiroideo,

leucemia linfoblástica de células T, leucemia mielógena crónica, leucemia linfocítica crónica, leucemia de células pilosas, leucemia linfoblástica aguda, leucemia mielógena aguda, leucemia neutrofílica crónica, leucemia de células T linfoblástica aguda, plasmacitoma, leucemia inmunoblástica de células grandes, leucemia de células del manto, mieloma múltiple, leucemia megacariobástica, mieloma múltiple, leucemia megacariocítica aguda, leucemia promielocítica, eritroleucemia,

linfoma maligno, linfoma de hodgkin, linfoma no Hodgkin, linfoma linfoblástico de células T, linfoma de Burkitt, linfoma folicular,

neuroblastoma, cáncer de vejiga, cáncer urotelial, cáncer de pulmón, cáncer vulvar, cáncer cervical, cáncer endometrial, cáncer renal, mesotelioma, cáncer esofágico, cáncer de las glándulas salivales, cáncer hepatocelular, cáncer gástrico, cáncer nasofaríngeo, cáncer oral, cáncer de la boca, GIST (tumor estromático gastrointestinal) y cáncer testicular.

Convenientemente, la presente invencion se refiere a un método para tratar o reducir la gravedad de un cáncer seleccionado entre: cerebral (gliomas), glioblastomas, síndrome de Bannayan-Zonana, enfermedad de Cowden, enfermedad de Lhermitte-Duclos, de mama, de colon, de cabeza y cuello, de riñón, de pulmón, de hígado, melanoma, de ovario, pancreático, de próstata, sarcoma y tiroideo.

Convenientemente, la presente invención se refiere a un método para tratar o reducir la gravedad de un cáncer seleccionado entre cáncer de ovarios, mama, páncreas y de próstata.

Aislamiento y Purificación de AKT1 con señal His (aa 136-480)

Se lisaron células de insecto que expresaban AKT1 señalizada con His (aa 136-480) en HEPES 25 mM, NaCl 100 mM, imidazol 20 mM; pH 7,5, usando un polytron (5 ml de tampón de lisis/g de células). Se retiraron los desechos celulares por centrifugación a 28.000 x *g* durante 30 minutos. El sobrenadante se filtró a través de un filtro de 4,5 micrómetros y después se cargó sobre una columna quelante de níquel pre-equilibrada con tampón de lisis. La columna se lavó con 5 volúmenes de columna (CV) de tampón de lisis y después con 5 CV de tampón B al 20%, siendo el tampón B HEPES 25 mM, NaCl 100 mM, imidazol 300 mM; pH 7,5. La AKT1 marcada con His (aa 136-480) se eluyó con un gradiente lineal de 20-100% de tampón B sobre 10 CV. Se reunieron las fracciones de elución de AKT1 marcada con His (136-480) y se diluyeron 3 veces con tampón C, siendo el tampón C HEPES 25 mM, pH 7,5. Después, la muestra se cromatografió sobre una columna de Q-Sepharose HP pre-equilibrada con tampón C. La columna se lavó con 5 CV de tampón C y después se eluyó por etapas con 5 CV de D al 10%, 5 CV de D al 20%, 5 CV de D al 30%, 5 CV de D al 50% y 5 CV de D al 100%; donde el tampón D es HEPES 25 mM, NaCl 1000 mM; pH 7,5. Se reunieron las fracciones que contenían AKT1 marcada con His (aa 136-480) y se concentraron en un concentrador con un límite de peso molecular de 10 kDa. La AKT1 marcada con His (aa 136-480) se cromatografió sobre una columna de exclusión molecular Superdex 75 pre-equilibrada con HEPES 25 mM, NaCl 200 mM, DTT 1 mM; pH 7,5. Las fracciones de AKT1 marcada con His (aa 136-480) se examinaron usando SDS-PAGE y espectrometría de masas. La proteína se reunió, se concentró y se congeló a -80°C.

Se aislaron AKT2 marcada con His (aa 138-481) y AKT3 marcada con His (aa 135-479) y se puificaron de una manera similar.

Ensayo Enzimático de AKT marcada con His

Se ensayaron compuestos de la presente invención con respecto a la actividad inhibidora de la proteína serina quinasa AKT 1, 2 y 3 en ensayos de fosforilación de sustratos. Este ensayo examina la capacidad de compuestos orgánicos de molécula pequeña para inhibir la fosforilación de serina de un sustrato peptídico. Los ensayos de fosforilación de sustrato usan los dominios catalíticos de

AKT 1, 2 ó 3. AKT 1, 2 y 3 también están disponibles en el mercado en Upstate USA, Inc. El método mide la capacidad de la enzima aislada de catalizar la transferencia del gamma-fosfato desde el ATP al resto de serina de un péptido sintético biotinilado de SEC. ID Nº: 1 (Biotina-ahx-ARKRERAYSFGHHA-amida). La fosforilación del sustrato se detectó por el siguiente procedimiento:

Los ensayos se realizaron en placas blancas de fondo en U de 384 pocillos. Se incubó enzima AKT activada 10 nM durante 40 minutos a temperatura ambiente en un volumen de ensayo de 20 µl que contenía MOPS 50 mM, pH 7,5, $MgCl_2$ 20 mM, ATP 4 µM, péptido 8 µM, 0,04 µCi [g-^{33}P] de ATP/pocillo, CHAPS 1 mM, DTT 2 mM y 1 µl de compuesto de ensayo en DMSO al 100%. La reacción se interrumpió mediante la adición de 50 µl de mezcla de perlas SPA (PBS de Dulbecco sin Mg^{2+} y Ca^{2+}, Triton X-100 al 0,1%, EDTA 5 mM, ATP 50 µM, 2,5 mg/ml de perlas SPA recubiertas con estreptavidina.) La placa se selló, las perlas se dejaron sedimentar durante una noche, y después la placa se sometió a recuento en un Packard Topcount Microplate Scintillation Counter (Packard Instrument Co., Meriden, CT).

Los datos para las respuestas a las dosis se representaron como % de control calculado con la fórmula de reducción de datos 100*(U1-C2)/(C1-C2) frente a la concentración de compuesto, donde U es el valor desconocido, C1 es el valor medio de control obtenido para DMSO, y C2 es el valor medio de control obtenido para EDTA 0,1 M. Los datos se ajustan a la curva descrita por: y = ((Vmax * x)/(K + x)) donde Vmax es la asíntota superior y K es la CI50.

Clonación de AKT1 humana de longitud completa (FL):

Se amplificó el gen AKT1 humano de longitud completa por PCR a partir de un plásmido que contenía AKT1-ER miristilado (donación de Robert T. Abraham, Duke University según la MTA, descrito en Klippel et al. en Molecular and Cellular Biology 1998 Volumen 18 p.5699) usando el cebador 5': SEC.ID Nº: 1, 5' TATATAGGATCCATGAGCGACGTGGC 3' y el cebador 3': SEC.ID Nº: 2, AAATTTCTCGAGTCAGGCCGTGCTGCTGG 3'. El cebador 5' incluía un sitio BamHI y el cebador 3' incluía un sitio XhoI para la clonación. El producto de PCR resultante se subclonó en pcDNA3 como un fragmento BamHI/XhoI. Una mutación en la secuencia (TGC) que codifica una Cisteína^{25} se convirtió en la secuencia

AKT1 de tipo silvestre (CGC) que codificaba una Arginina^{25} por mutagénesis dirigida usando el Kit de Mutagénesis Dirigida QuikChange® (Stratagene). El cebador mutagénico AKT1: SEC.ID Nº: 3, 5' ACCTGGCGGCCACGCTACTTCCTCC y el cebador de selección: SEC.ID Nº: 4, 5' CTCGAGCATGCAACTAGAGGGCC (diseñados para destruir un sitio XbaI en el sitio de clonación múltiple de pcDNA3) se usaron de acuerdo con las sugerencias del fabricante. Para los fines de expresión/purificación, AKT1 se aisló como un fragmento BamHI/XhoI y se clonó en los sitios BamHI/XhoI de pFastbacHTb (Invitrogen).

Expresión de AKT1 humana FL:

La expresión se realizó usando el Sistema de Expresión de Baculovirus BAC-to-BAC de Invitrogen (nº de catálogo 10359-016). En resumen 1) el ADNc se transfirió desde el vector FastBac a ADN de bácmido, 2) el ADN de bácmido se aisló y se usó para transfectar células de insecto Sf9, 3) el virus se produjo en células Sf9, 4) se infectaron células T. ni con este virus y se enviaron para la purificación.

Purificación de AKT1 humana FL:

Para la purificación de AKT1 de longitud completa, se resuspendieron 130 g de células sf9 (lote nº 41646W02) en tampón de lisis (tampón A, 1 l, pH 7,5) que contenía HEPES 25 mM, NaCl 100 mM e imidazol 20 mM. La lisis celular se realizó por Avestin (2 pases a 15K-20K psi (103,39-137,86 MPa)). El desecho celular se retiró por centrifugación a 16K rpm durante 1 hora y el sobrenadante se unió por lotes a perlas de HP Nickel Sepharose de 10 ml a 4ºC durante una noche. Las perlas después se transfirieron a la columna y el material unido se eluyó con tampón B (HEPES 25 mM, NaCl 100 mM e imidazol 300 mM, pH 7,5). Las fracciones de elución de AKT se reunieron y se diluyeron 3 veces usando tampón C (HEPES 25 mM y DTT 5 mM; pH 7,5). La muestra se filtró y se cromatografió sobre una columna Q-HP de 10 ml pre-equilibrada con tampón C a 2 ml/min.

La columna Q-HP se lavó con 3 volúmenes de columna (CV) de tampón C, y en la siguiente etapa se eluyó con 5 CV de D al 10%, 5 CV de D al 20%, 5 CV de

D al 30%, 5 CV de D al 50% y 5 CV de D al 100%; siendo el tampón D HEPES 25 mM, NaCl 1000 mM y DTT 5 mM; pH 7,5. Se recogieron fracciones de 5 ml. Las fracciones que contenían AKT se reunieron y se concentraron a 5 ml. La proteína después se introdujo en una columna de clasificación por tamaños Superdex 75 de 120 ml que se pre-equilibró con HEPES 25 mM, NaCl 200 mM, DTT 5 mM; pH 7,5. Se recogieron fracciones de 2,5 ml.

Se reunieron las fracciones que eluían AKT 1, se extrajeron alícuotas (1 ml) y se almacenaron a –80C. Se usaron espectrometría de masas y SDS-PAGE para confirmar la pureza y la identidad de la AKT1 de longitud completa purificada.

Se clonaron la AKT2 de longitud completa y AKT3 de longitud completa, se expresaron y se purificaron de una manera similar.

Ensayo Enzimático de AKT

Los compuestos de la presente invención se ensayan con respecto a la actividad inhibidora de proteína serina quinasa AKT 1, 2, y 3 en ensayos de fosforilación de sustratos. Este ensayo examina la capacidad de compuestos orgánicos de molécula pequeña para inhibir la fosforilación de serina de un sustrato peptídico. Los ensayos de fosforilación de sustrato usan los dominios catalíticos de AKT 1, 2 ó 3, AKT 1, 2 y 3 también están disponibles en el mercado en Upstate USA, Inc. El método mide la capacidad de la enzima aislada de catalizar la transferencia del gamma-fosfato desde el ATP al resto de serina de un péptido sintético biotinilado SEC. ID Nº: 5 (Biotina-ahx-ARKRERAYSFGHHA-amida). La fosforilación del sustrato se detecta por el siguiente procedimiento:

Los ensayos se realizan en placas blancas de fondo en U de 384 pocillos. Se incuba una concentración 10 nM de enzima AKT activada durante 40 minutos a temperatura ambiente en un volumen de ensayo de 20 µl que contenía MOPS 50 mM, pH 7,5, $MgCl_2$ 20 mM, ATP 4 µM, péptido 8 µM, 0,04 µCi de [g-^{33}P] ATP/pocillo, CHAPS 1 mM, DTT 2 mM y 1 µl de compuesto de ensayo en DMSO al 100%. La reacción se detiene mediante la adición de 50 µl de mezcla de perlas SPA (PBS de Dulbecco sin Mg^{2+} y Ca^{2+}, Tritón X-100 al 0,1%, EDTA 5 mM, ATP 50 µM y 2,5 mg/ml de perlas SPA recubiertas con estreptavidina). La placa se cierra herméticamente, se deja que sedimenten las perlas durante una noche y después

la placa se cuenta en un Contador de Centelleo Packard Topcount Microplate (Packard Instrument Co., Meriden, CT).

Los datos para las respuestas a la dosis se representan como % de control calculado con la fórmula de reducción de datos 100*(U1-C2)/(C1-C2) frente a la concentración de compuesto, donde U es el valor desconocido, C1 es el valor de control medio obtenido para DMSO y C2 es el valor de control medio obtenido para EDTA 0,1 M. Los datos se ajustan a la curva descrita por: y = ((Vmax * x)/(K + x)) donde Vmax es la asíntota superior y K es la CI50.

Los compuestos de la invención se ensayan con respecto a la actividad contra AKT1, AKT2, y AKT3 en uno o más de los ensayos anteriores.

La mayoría de los compuestos de los Ejemplos se ensayaron, en general, de acuerdo con los ensayos de la enzima AKT anteriores y en al menos un ensayo experimental presentaron un valor de pCI50: ≥5,9 contra la AKT1 de longitud completa; ≥5,0 contra la AKT2 de longitud completa; y ≥5,0 contra la AKT3 de longitud completa.

Los compuestos de los Ejemplos 31, 32, 91, 95, 120, 128, 140, 161, 167, 169, 170, 190, 222, 225, 237, 249, 258 y 259 se ensayaron, en general, de acuerdo con los ensayos de la enzima AKT anteriores y en al menos un ensayo experimental presentaron un valor de pCI50: ≥8,6 contra la AKT1 de longitud completa; y ≥7,5 contra la AKT2 de longitud completa. La mayoría de los compuestos de los Ejemplos 31, 32, 91, 95, 120, 128, 140, 161, 167, 169, 170, 190, 222, 225, 237, 249, 258 y 259 se ensayaron, en general, de acuerdo con los ensayos de la enzima AKT anteriores y en al menos un ensayo experimental presentaron un valor de pCI50; ≥7,6 contra la AKT3 de longitud completa.

El compuesto del Ejemplo 96 se ensayó, en general, de acuerdo con el ensayo de la enzima AKT anterior y en al menos un ensayo experimental presentó un valor de pCI50: igual a 9,0 contra la AKT1 de longitud completa; igual a 8,0 contra la AKT2 de longitud completa; e igual a 8,8 contra la AKT3 de longitud completa.

El compuesto del Ejemplo 137 se ensayó, en general, de acuerdo con el ensayo de la enzima AKT anterior y en al menos un ensayo experimental presentó un valor de pCI50: igual a 9,0 contra la AKT1 de longitud completa; igual a 7,8 contra la AKT2 de longitud completa; e igual a 8,4 contra la AKT3 de longitud completa.

El compuesto del Ejemplo 224 se ensayó, en general, de acuerdo con los ensayos de la enzima AKT anteriores y en al menos un ensayo experimental presentó un valor de pCI50: igual a 8,7 contra la AKT1 de longitud completa; e igual a 7,8 contra la AKT2 de longitud completa.

En los datos anteriores, pCI50 se define como el -log(CI50) donde el valor de CI50 se expresa en unidades molares.

Los compuestos farmacéuticamente activos dentro del alcance de esta invención son útiles como inhibidores de AKT en mamíferos, particularmente seres humanos, que lo necesiten.

Por lo tanto, la presente invención proporciona un método para tratar cáncer, artritis y otras afecciones que requieren inhibición de la AKT, que comprende administrar un compuesto eficaz de Fórmula (I) y/o una sal farmacéuticamente aceptable, hidrato, solvato o profármaco del mismo. Los compuestos de Fórmula (I) también proporcionan un método para tratar los estados de enfermedad indicados anteriormente debido a su capacidad demostrada de actuar como inhibidores de Akt. El fármaco puede administrarse a un paciente que lo necesite por cualquier vía de administración convencional, incluyendo, pero sin limitarse a la vía intravenosa, intramuscular, oral, subcutánea, intradérmica y parenteral.

Los compuestos farmacéuticamente activos de la presente invención se incorporan en formas de dosificación convenientes tales como cápsulas, comprimidos o preparaciones inyectables. Se emplean vehículos farmacéuticos sólidos o líquidos. Los vehículos sólidos incluyen almidón, lactosa, sulfato cálcico dihidratado, terra alba, sacarosa, talco, gelatina, agar, pectina, goma arábiga, estearato de magnesio y ácido esteárico. Los vehículos líquidos comprenden jarabe, aceite de cacahuete, aceite de oliva, solución salina y agua. De igual forma, el excipiente o diluyente puede incluir cualquier material de liberación prolongada, tal como monoestearato de glicerilo o diestearato de glicerilo, solo o con una cera. La cantidad de vehículo sólido varía ampliamente pero, preferiblemente, será de aproximadamente 25 mg a aproximadamente 1 g por unidad de dosificación. Cuando se usa un vehículo líquido, la preparación estará en forma de un jarabe, elixir, emulsión, cápsula de gelatina blanda, líquido inyectable estéril tal en forma de una ampolla, o una suspensión líquida acuosa o no acuosa.

Las preparaciones farmacéuticas se obtienen siguiendo técnicas convencionales de un químico farmacéutico que implican mezcla, granulación y compresión, cuando sea necesario, para las formas de comprimidos, o mezcla, relleno y disolución de los ingredientes, cuando sea apropiado, para dar los productos orales o parenterales deseados.

La dosis de los compuestos farmacéuticamente activos de la presente invención en una unidad de dosificación farmacéutica como se ha descrito anteriormente será una cantidad eficaz no tóxica, preferiblemente seleccionada entre el intervalo de 0,001 a 100 mg/kg de compuesto activo, preferiblemente de 0,001 a 50 mg/kg. Cuando se trata a un paciente humano que necesita un inhibidor de Akt, la dosis seleccionada se administra preferiblemente de 1 a 6 veces al día, por vía oral o parenteral. Las formas preferidas de administración parenteral incluyen la vía tópica, rectal, transdérmica, por inyección y continuamente por infusión. Las unidades de dosificación oral para la administración humana preferiblemente contienen de 0,05 a 3500 mg de compuesto activo. Se prefiere la administración oral, que usa dosificaciones inferiores. Sin embargo, también puede usarse la administración parenteral, a dosis superiores, cuando sea seguro y conveniente para el paciente.

Las dosificaciones óptimas a administrar pueden determinarse fácilmente por los especialistas en la técnica, y variarán con el inhibidor de Akt particular que se esté usando, la concentración de la preparación, el modo de administración y el avance del estado de enfermedad. Otros factores que dependen del paciente particular que se está tratando requerirán ajustar las dosificaciones, incluyendo la edad del paciente, el peso, la dieta y el momento de la administración.

El método de esta invención para inducir actividad inhibidora de Akt en mamíferos, incluyendo seres humanos, comprende administrar a un sujeto que necesite dicha actividad una cantidad inhibidora de Akt eficaz de un compuesto farmacéuticamente activo de la presente invención.

La invención también proporciona el uso de un compuesto de Fórmula (I) en la fabricación de un medicamento para uso como un inhibidor de Akt.

La invención también proporciona el uso de un compuesto de Fórmula (I) en la fabricación de un medicamento para uso en terapia.

La invención también proporciona el uso de un compuesto de Fórmula (I) en la fabricación de un medicamento para uso en el tratamiento de cáncer.

La invención también proporciona el uso de un compuesto de Fórmula (I) en la fabricación de un medicamento para uso en el tratamiento de la artritis.

La invención también proporciona una composición farmacéutica para uso como un inhibidor de Akt que comprende un compuesto de Fórmula (I) y un vehículo farmacéuticamente aceptable.

La invención también proporciona una composición farmacéutica para uso en el tratamiento de cáncer que comprende un compuesto de Fórmula (I) y un vehículo farmacéuticamente aceptable.

La invención también proporciona una composición farmacéutica para uso en el tratamiento de la artritis que comprende un compuesto de Fórmula (I) y un vehículo farmacéuticamente aceptable.

No se esperan efectos toxicológicos inaceptables cuando los compuestos de la invención se administran de acuerdo con la presente invención.

Además, los compuestos farmacéuticamente activos de la presente invención pueden co-administrarse con otros ingredientes activos, tales como otros compuestos conocidos para tratar el cáncer o la artritis, o compuestos conocidos por tener utilidad cuando se usan junto con un inhibidor de Akt.

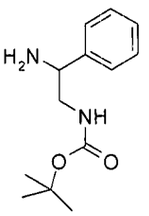
Sin mayor elaboración, se cree que un especialista en la técnica, utilizando la anterior descripción, puede utilizar la presente invención en su grado más completo. Por lo tanto, los siguientes ejemplos deben considerarse simplemente ilustrativos y de ninguna manera limitantes del alcance de la presente invención.

Detalles Experimentales

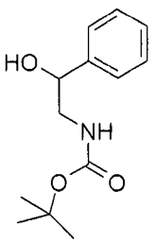
Los compuestos de los Ejemplos 1 a 328 se preparan fácilmente de acuerdo con los Esquemas 1 a 3 o por métodos análogos.

Preparación 1

Preparación de (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo

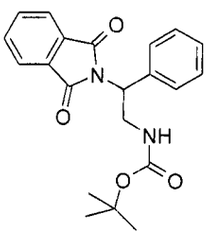


a) (2-hidroxi-2-feniletil)carbamato de 1,1-dimetiletilo



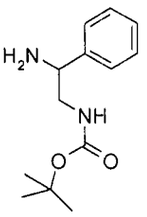
A una solución de 2-amino-1-feniletanol (5 g, 36,4 mmol) en THF (182 ml) a 25°C se le añadió en una porción Boc_2O (8,7 g, 40,1 mmol). Después de 0,5 h, la solución se concentró y el residuo se usó directamente sin purificación adicional: LC-MS (ES) m/z = 238 $(M+H)^+$.

b) [2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-feniletil]carbamato de 1,1-dimetiletilo



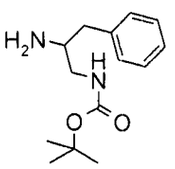
A una solución de (2-hidroxi-2-feniletil)carbamato de 1,1-dimetiletilo (2 g, 8,44 mmol), ftalimida (1 g, 7,03 mmol) y trifenilfosfina (2,76 g, 10,5 mmol) en THF (35 ml) a 25°C se le añadió gota a gota DEAD (1,7 ml, 10,5 mmol). Después de 0,5 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 15% en hexanos), produciendo el compuesto del título (2 g, 80%) en forma de una espuma de color blanco: LC-MS (ES) m/z = 367 $(M+H)^+$.

c) (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo



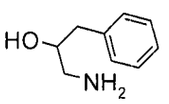
Una solución de [2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-feniletil]carbamato de 1,1-dimetiletilo (2 g, 5,46 mmol) y $MeNH_2$ (al 40% en peso en H_2O, 10 equiv.) o NH_2NH_2 (10 equiv.) en MeOH (0,5M, 10 ml) se calentó a 60°C en un tubo cerrado herméticamente. Después de 12 h, la solución se concentró y se purificó por cromatografía en columna (carga seca de sílice, MeOH al 2% en DCM (NH_4OH al 1%)), produciendo el compuesto del título (1,1 g, 85%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 237 $(M+H)^+$.

Preparación 2



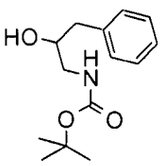
Preparación de (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo

a) 1-amino-3-fenil-2-propanol



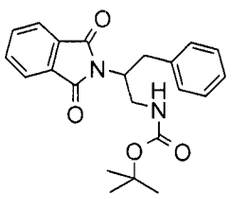
Una solución de 2-(fenilmetil)oxirano (7,5 g, 56,3 mmol) en NH_4OH (100 ml) se agitó a 25°C en un tubo cerrado herméticamente. Después de 12 h, la solución se concentró y se usó directamente: LCMS (ES) m/e 152 $(M+H)^+$.

b) (2-hidroxi-3-fenilpropil)carbamato de 1,1-dimetiletilo



A una solución de 1-amino-3-fenil-2-propanol (7,6 g, 50 mmol) en THF (50 ml) a TA se le añadió $(Boc)_2O$ (12,0 g, 55 mmol). Después de agitar a TA durante 2 h, la solución de reacción se concentró al vacío y el residuo se purificó sobre gel de sílice (MeOH al 5% en DCM (NH_4OH al 0,5%)), produciendo el compuesto del título (13,1 g, 91%) en forma de un aceite de color amarillo transparente: LCMS (ES) m/z 252 $(M+H)^+$.

c) [2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-3-fenilpropil]carbamato de 1,1-dimetiletilo

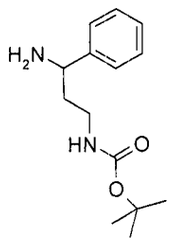


A una solución de (2-hidroxi-3-fenilpropil)carbamato de 1,1-dimetiletilo (10,0 g, 39,8 mmol), PPh_3 (12,5 g, 47,8 mmol) y ftalimida (6,44 g, 43,8 mmol) en THF (125 ml) a TA se le añadió DEAD (9,4 ml, 59,7 mmol) durante 5 min. Después de 1 h a TA, la solución de reacción se concentró y se purificó sobre sílice (hexanos/EtOAc, 2:1) para dar el compuesto del título en forma de un sólido de color blanco (12,6 g, 83%): LCMS (ES) m/z 381 $(M+H)^+$.

d) (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo

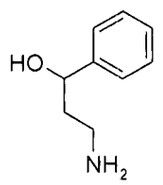
Se añadió NH_2NH_2 (12,5 ml, 394 mmol) a una solución en THF/MeOH (50 ml/50 ml) de (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo (7,5 g, 19,7 mmol) y la mezcla se agitó a 50°C en un sistema cerrado herméticamente. Después de 12 horas, los sólidos se filtraron, lavando con metanol. El filtrado se concentró y se purificó por cromatografía en columna usando MeOH al 5% en $CHCl_3$ que contenía NH_4OH al 0,5% para dar el compuesto del título (3;75 g, 76%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 251 $(M+H)^+$.

Preparación 3



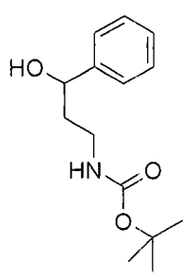
Preparación de (3-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo

a) 3-amino-1-fenil-1-propanol



Se añadió gota a gota benzoilacetonitrilo (2 g, 13,8 mmol) en THF (35 ml) mediante un embudo de adición a una solución a 0°C de LAH (1,6 g, 41,3 mmol) en THF (35 ml). La solución resultante se calentó a 25°C y después se calentó a 60°C durante 2 h más. Después de enfriar a 0°C, se añadió gota a gota una solución saturada de tartrato sódico potásico y la solución se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en columna (sílice, MeOH al 5-8% en DCM (NH_4OH al 1%)), produciendo el amino alcohol (1,4 g, 67%) en forma de un aceite transparente: LCMS (ES) m/z 152 $(M+H)^+$.

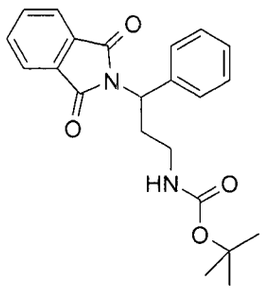
b) (3-hidroxi-3-fenilpropil)carbamato de 1,1-dimetiletilo



Se disolvió 3-amino-1-fenil-1-propanol (1,4 g, 9,27 mmol) en THF (50 ml) y se añadió en una porción Boc_2O (2,4 g, 11,1 mmol). Después de 30 min, la solución

se concentró y el residuo se purificó a través de sílice (MeOH al 0,5-1% en DCM (NH_4OH al 1%)), produciendo el compuesto del título (1,6 g, 69%) en forma de un sólido de color blanco pálido: LCMS (ES) m/z 152 $(M+H)^+$.

c) [3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-fenilpropil]carbamato de 1,1-dimetiletilo

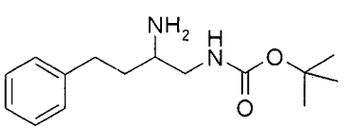


A una solución de (3-hidroxi-3-fenilpropil)carbamato de 1,1-dimetiletilo (3 g, 11,95 mmol), PPh_3 (4 g, 15,5 mmol) y ftalimida (1,8 g, 11,95 mmol) en THF (60 ml) a TA se le añadió DEAD (2,4 ml, 15,5 mmol) durante 5 min. Después de 1 h a TA, la solución de reacción se concentró y se purificó sobre sílice (hexanos/EtOAc, 4:1) para dar el compuesto del título en forma de un sólido de color blanco (2,2 g, 48%): LCMS (ES) m/z 381 $(M+H)^+$.

c) (3-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo

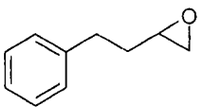
Se añadió NH_2NH_2 (1,8 ml, 57,7 mmol) a una solución en THF/MeOH (1:1, 30 ml) de [3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-3-fenilpropil]carbamato de 1,1-dimetiletilo (2,2 g, 5,79 mmol) y la mezcla se agitó a 50°C en un sistema cerrado herméticamente. Después de 12 horas, los sólidos se filtraron, lavando con metanol. El filtrado se concentró y se purificó por cromatografía en columna usando MeOH al 5% en $CHCl_3$ que contenía NH_4OH al 1% para dar el compuesto del título (1,1 g, 76%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 251 $(M+H)^+$.

Preparación 4



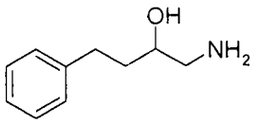
Preparación de (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo

a) 2-(2-feniletil)oxirano



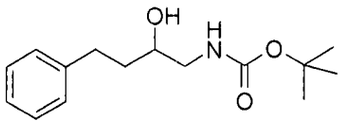
Se añadió en una porción ácido 3-clorobencenocarboperoxoico (12,1 g, 54,0 mmol) a una solución de 3-buten-1-ilbenceno (7,15 g, 54,1 mmol) en CH_2Cl_2 a 0°C seguido de calentamiento a 25°C durante una noche. Se añadió $NaHCO_3$ saturado, la mezcla se separó y el aceite transparente resultante (8,0 g, cuant.) se usó a continuación sin purificación adicional: LC-MS (ES) m/z = 149 $(M+H)^+$.

b) 1-amino-4-fenil-2-butanol



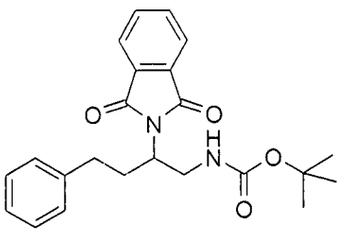
Se puso 2-(2-feniletil)oxirano (8,0 g, 54 mmol) en un tubo cerrado herméticamente con NH_3 7 N-MeOH (130 ml) y la mezcla se agitó 2 horas a 70°C seguido de concentración para dar un aceite transparente (que se usó sin purificación adicional en la siguiente etapa).

c) (2-hidroxi-4-fenilbutil)carbamato de 1,1-dimetiletilo



Se disolvió 1-amino-4-fenil-2-butanol (7,4 g, 50,0 mmol) en THF (50 ml) y se añadió en una porción Boc_2O (13 g, 59,6 mmol). Después de 30 min, la solución se concentró y el residuo se purificó a través de un lecho de sílice (MeOH al 5% en DCM (NH_4OH al 0,5%)), produciendo el compuesto del título (13,1 g, 91%) en forma de un aceite de color amarillo transparente: LCMS (ES) m/z 266 $(M+H)^+$.

d) [2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-4-fenilbutil]carbamato de 1,1-dimetiletilo

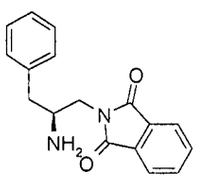


A una solución de (2-hidroxi-4-fenilbutil)carbamato de 1,1-dimetiletilo (3,0 g, 11,4 mmol), PPh_3 (3,6 g, 13,7 mmol) y ftalimida (1,84 g, 12,5 mmol) en THF (60 ml) a TA se le añadió DEAD (1,8 ml, 11,4 mmol) durante 5 min. Después de 0,5 h a TA, la solución de reacción se concentró y se purificó sobre sílice (hexanos/EtOAc, 2:1) para dar el compuesto del título en forma de un sólido de color blanco (3,1 g, 69%): LCMS (ES) m/z 395 $(M+H)^+$.

e) (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo

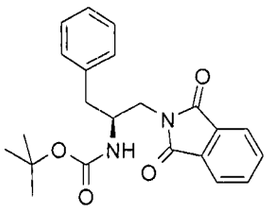
Se añadió NH_2NH_2 (2,5 ml, 79,6 mmol) a una solución en THF/MeOH (40 ml/40 ml) de (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo (3,1 g, 7,83 mmol) y la mezcla se agitó durante una noche. Después de 12 horas, la solución se concentró y se purificó por cromatografía en columna usando MeOH al 5% en $CHCl_3$ que contenía NH_4OH al 0,5% para dar el compuesto del título (1,4 g, 66%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparación 5



Preparación de 2-[(2*S*)-2-amino-3-fenilpropil]-1*H*-isoindolo-1,3(2*H*)-diona

a) [(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-(fenilmetil)etil]carbamato de 1,1-dimetiletilo

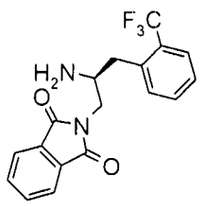


A una solución de (S)-(-)-2-(terc-butoxicarbonilamino)-3-fenil-1-propanol (3,0 g, 11,9 mmol), PPh_3 (3,74 g, 14,4 mmol) y ftalimida (1,93 g, 13,1 mmol) en THF (75 ml) a TA se le añadió DEAD (2,8 ml, 17,8 mmol) durante 5 min. Después de 1,5 h a TA, la solución de reacción se concentró y se purificó sobre sílice (hexanos/EtOAc, 2:1) para dar el compuesto del título en forma de un sólido de color blanco (4,3 g, 95%): LCMS (ES) m/z 381 $(M+H)^+$.

b) 2-[(2*S*)-2-amino-3-fenilpropil]-1*H*-isoindolo-1,3(2*H*)-diona

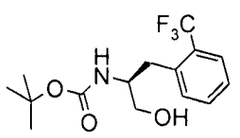
A una solución de [(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-(fenilmetil)etil]carbamato de 1,1-dimetiletilo (4,3 g, 11,3 mmol) en MeOH (100 ml) a TA se le añadió HCl 4 M en dioxano (50 ml). Después de agitar durante 3 h a TA, la solución de reacción se concentró para dar un sólido de color blanco (cuant.): LCMS (ES) m/z 281 $(M+H)^+$.

Preparación 6



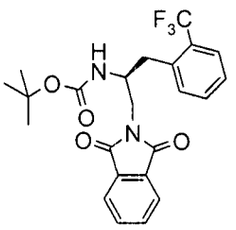
Preparación de 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona

a) ((1S)-2-hidroxi-1-{[2-(trifluorometil)fenil]metil}etil)carbamato de 1,1-dimetiletilo



A una solución de N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina (5 g, 15 mmol) en THF (75 ml) agitada a 0°C se le añadió BH_3-THF (45 ml, 45 mmol-1 M en THF). Después de 12 h, la reacción se interrumpió con AcOH:MeOH (1:5, 24 ml) y se repartió entre $NaHCO_3$ acuoso saturado y DCM. Después, la fase acuosa se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se usaron directamente (4,2 g, 88%): LCMS (ES) m/e 320 $(M+H)^+$.

b) ((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)carbamato de 1,1-dimetiletilo

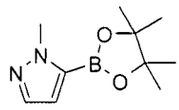


A una solución de ((1S)-2-hidroxi-1-{[2-(trifluorometil)fenil]metil}etil)carbamato de 1,1-dimetiletilo (4,2 g, 13,2 mmol), trifenilfosfina (4,5 g, 17,1 mmol) y ftalimida (1,9 g, 13,2 mmol) en THF (66 ml) a 25°C se le añadió azodicarboxilato de dietilo (2,7 ml, 17,1 mmol). Después de agitar a TA durante 1 h, la solución de reacción se concentró al vacío y el residuo se purificó sobre gel de sílice (MeOH al 1% en DCM), produciendo el compuesto del título (3,2 g, 54%) en forma de un sólido de color blanco: LCMS (ES) m/z 449 $(M+H)^+$.

c) 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona

A una solución de ((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)carbamato de 1,1-dimetiletilo (3,2 g, 7,1 mmol) en MeOH (35 ml) a TA se le añadió HCl 4 M en dioxano (18 ml). Después de 12 h, la solución se concentró, produciendo el compuesto del título (2,7 g, cuant.) en forma de la sal HCl: LCMS (ES) m/z 349 $(M+H)^+$.

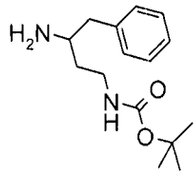
Preparación 7



Preparación de 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol

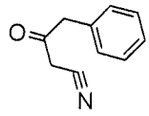
A una solución de 1-metilpirazol (4,1 g, 50 mmol) en THF (100 ml) a 0°C se le añadió n-BuLi (2,2 M en THF, 55 mmol). La solución de reacción se agitó durante 1 hora a TA y después se enfrió a -78°C [*J. Heterocyclic Chem.* 41, 931 (2004)]. A la solución de reacción se le añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (12,3 ml, 60 mmol). Después de 15 min a -78°C, la reacción se dejó calentar a 0°C durante 1 hora. La reacción se diluyó con una solución saturada de NH_4Cl y se extrajo con DCM. Las fracciones orgánicas se lavaron con H_2O (2 x 100 ml), se secaron sobre Na_2SO_4 y se concentraron al vacío para producir un sólido de color castaño (8,0 g, 77%) que se usó sin purificación adicional. LCMS (ES) m/z 127 $(M+H)^+$ para $[RB(OH)_2]$; ^1H RMN ($CDCl_3$, 400 MHz) 7,57 (s, 1H), 6,75 (s, 1H), 4,16 (s, 3H) y 1,41 (s, 12H).

Preparación 8



Preparación de (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo

a) 3-oxo-4-fenilbutanonitrilo



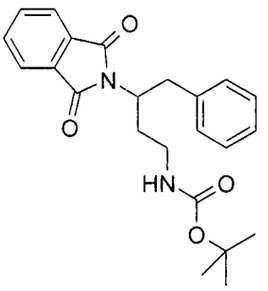
A una solución de ácido cianoacético (2 g, 23,5 mmol) en THF (100 ml) a -78°C se le añadió nBuLi (10 ml, 25,9 mmol, 2,5 M en hexanos). Después de 30 min, se añadió gota a gota cloruro de fenilacetilo (1,6 ml, 11,8 mmol). Después de 30 min más, la solución se repartió entre HCl 1 N y Et_2O y la fase acuosa se lavó varias veces con Et_2O. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice,

EtOAc al 30% en hexanos), produciendo el compuesto del título (770 mg, 40%) en forma de un aceite de color castaño: LCMS (ES) m/z 160 $(M+H)^+$.

b) (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo

Una solución de 3-oxo-4-fenilbutanonitrilo (1,1 g, 6,92 mmol) en THF (10 ml) se añadió a una solución a 0°C de hidruro de litio y aluminio (787 mg, 20,8 mmol) en THF (25 ml). Después de 12 h, la solución se inactivó con H_2O (943 µl), NaOH 6 N (716 µl) y H_2O (3,5 ml). El precipitado resultante se filtró y el lecho se lavó varias veces con DCM. El filtrado se concentró, después se disolvió de nuevo en THF (30 ml) y se añadió en una porción Boc_2O (1,5 g, 6,92 mmol). Después de 30 min, la solución se concentró y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título (1 g, 55%-2 etapas) en forma de un sólido de color naranja: LCMS (ES) m/z 265 $(M+H)^+$.

c) [3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-4-fenilbutil]carbamato de 1,1-dimetiletilo



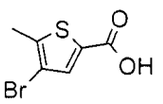
A una solución de (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo (1 g, 3,77 mmol), PPh_3 (1,3 g, 4,91 mmol) y ftalimida (555 mg, 3,77 mmol) en THF (18 ml) a TA se le añadió DEAD (772 µl, 4,91 mmol) durante 5 min. Después de 1 h a TA, la solución de reacción se concentró y se purificó sobre sílice (hexanos/EtOAc, 5:1) para dar el compuesto del título en forma de un sólido de color blanco (725 mg, 49%): LCMS (ES) m/z 395 $(M+H)^+$.

d) (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo

Se añadió NH_2NH_2 (577 µl, 18,4 mmol) a una solución en THF/MeOH (1:1, 10 ml) de [3-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-4-fenilbutil]carbamato de 1,1-

dimetiletilo (725 mg, 1,84 mmol) y la mezcla se agitó a 50°C en un sistema cerrado herméticamente. Después de 12 horas, los sólidos se filtraron, lavando con metanol. El filtrado se concentró y se purificó por cromatografía en columna usando MeOH al 5% en $CHCl_3$ que contenía NH_4OH al 1% para dar el compuesto del título (483 mg, cuant.) en forma de un sólido de color blanco: LC-MS (ES) m/z = 264 $(M+H)^+$.

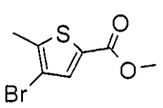
Preparación 9



Preparación de ácido 4-bromo-5-metil-2-tiofenocarboxílico

Una solución de bromo (725 µl, 14,1 mmol) en AcOH (2,8 ml) se añadió gota a gota a ácido 5-metil-2-tiofenocarboxílico (2 g, 14,1 mmol) y $FeCl_3$ (456 mg, 2,81 mmol) en AcOH (28 ml) a 25°C. Después de 5 h, la solución se vertió en hielo y el precipitado se filtró y se lavó con agua, produciendo el compuesto del título (3 g, cuant.) en forma de un polvo de color amarillo: LCMS (ES) m/z 222 $(M+H)^+$.

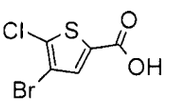
Preparación 10



Preparación de 4-bromo-5-metil-2-tiofenocarboxilato de metilo

Una solución de ácido 4-bromo-5-metil-2-tiofenocarboxílico (3 g, 13,6 mmol) en MeOH (67 ml) y H_2SO_4 (3 ml) se agitó a 50°C. Después de 12 h, a la solución se le añadió hielo-H_2O y el valor del pH se ajustó a ~11. La fase acuosa se extrajo varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente, produciendo el compuesto del título (3 g, 94%) en forma de un sólido de color naranja: LCMS (ES) m/z 236 (M+H)+.

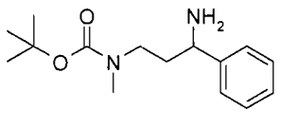
Preparación 11



Preparación de ácido 4-bromo-5-cloro-2-tiofenocarboxílico

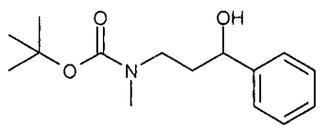
Una solución de bromo (634 µl, 12,3 mmol) en AcOH (2,5 ml) se añadió gota a gota a ácido 5-cloro-2-tiofenocarboxílico (2 g, 12,3 mmol) y $FeCl_3$ (399 mg, 2,50 mmol) en AcOH (25 ml) a 25ºC. La mezcla de reacción se calentó a reflujo, momento en el que se añadieron más cantidad de bromo (634 µl, 12,3 mmol) y $FeCl_3$ (399 mg, 2,50 mmol). Después de 7 d, la solución se vertió en hielo y el precipitado se filtró y se lavó con agua, produciendo el compuesto del título (3 g, cuant.) en forma de un polvo de color amarillo: LCMS (ES) m/z 242 $(M+H)^+$.

Preparación 12



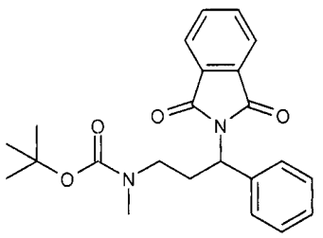
Preparación de (3-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo

a) (3-hidroxi-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo



Se disolvió 3-(metilamino)-1-fenil-1-propanol (4,12 g, 24,9 mmol) en THF (30 ml) y se añadió en una porción Boc_2O (1M/THF, 30 ml, 30 mmol). Después de 30 min, la solución se concentró y el residuo se purificó a través de un lecho de sílice (MeOH al 5% en DCM (NH_4OH al 0,5%)), produciendo el compuesto del título (6,4 g, 97%) en forma de un aceite de color amarillo transparente: LCMS (ES) m/z 265 $(M+H)^+$.

b) [3-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-3-fenilpropil]metilcarbamato de 1,1-dimetiletilo

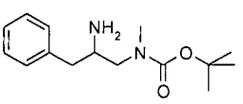


A una solución de (3-hidroxi-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo (2,8 g, 10,4 mmol), PPh_3 (3,3 g, 12,7 mmol) y ftalimida (1,86 g, 12,6 mmol) en THF (50 ml) a TA se le añadió DEAD (1,98 ml, 12,6 mmol) durante 5 min. Después de 0,5 h a TA, se añadió MeOH (10 ml) y la solución de reacción se absorbió sobre sílice y se purificó por cromatografía (hexanos/EtOAc, 2:1) para dar el compuesto del título en forma de un sólido de color blanco (2,7 g, 65%): LCMS (ES) m/z 395 $(M+H)^+$.

c) (3-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo

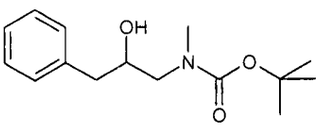
Se añadió NH_2NH_2 (1,7 ml, 54,2 mmol) a una solución en THF/MeOH (50 ml/10 ml) de [3-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-3-fenilpropil]metilcarbamato de 1,1-dimetiletilo (2,7 g, 6,8 mmol) y la mezcla se agitó durante una noche. Después de 12 horas, la solución se absorbió sobre sílice y se purificó por cromatografía en columna usando MeOH al 5% en $CHCl_3$ que contenía NH_4OH al 0,5% para dar el compuesto del título (1,4 mg, 77%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparación 13



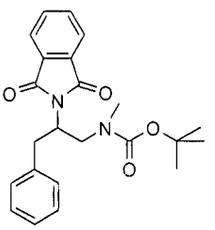
Preparación de (2-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo

a) (2-hidroxi-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo



A una solución de 1-(metilamino)-3-fenil-2-propanol (13 g, 78 mmol) [preparada de acuerdo con Galons, H. et al *Eur. J. Med. Chem. Chim. Ther.* **1979** 14, 165-170] en THF (390 ml) a TA se le añadió $(Boc)_2O$ (21,6 g, 99 mmol). Después de agitar a TA durante 2 h, la solución de reacción se absorbió sobre sílice y se purificó por cromatografía (EtOAc al 35%/Hex), produciendo el compuesto del título (11,6 g, 56%) en forma de un aceite de color amarillo transparente: LCMS (ES) m/z 266 $(M+H)^+$.

b) [2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-3-fenilpropil]metilcarbamato de 1,1-dimetiletilo



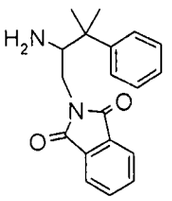
A una solución de (2-hidroxi-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo (11,6 g, 43,72 mmol), PPh_3 (14,3 g, 54,5 mmol) y ftalimida (8,7 g, 59,1 mmol) en THF (220 ml) a TA se le añadió DEAD (8,5 ml, 54 mmol) durante 15 min. Después de 0,5 h a TA, se añadió MeOH (10 ml) y la solución de reacción se absorbió sobre sílice y se purificó por cromatografía (hexanos/EtOAc, 2:1) para dar el compuesto del título en forma de un sólido de color blanco (9,97 g, 57%): LCMS (ES) m/z 395 $(M+H)^+$.

c) (2-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo

Se añadió NH_2NH_2 (7 ml, 0,2 mol) a una solución en THF/MeOH (100 ml/25 ml) de [2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-3-fenilpropil]metilcarbamato de 1,1-dimetiletilo (2,7 g, 6,8 mmol) y la mezcla se agitó durante una noche. Después de 12 horas, la solución se absorbió sobre sílice y se purificó por cromatografía en columna usando MeOH al 5% en $CHCl_3$ que contenía NH_4OH al 0,5% para dar el

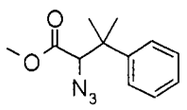
compuesto del título (5,8 mg, 88%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 265 $(M+H)^+$.

Preparación 14



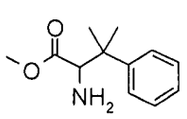
Preparación de 2-(2-amino-3-metil-3-fenilbutil)-1H-isoindolo-1,3(2H)-diona

a) 2-azido-3-metil-3-fenilbutanoato de metilo



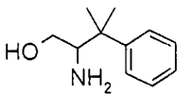
A una solución de KHMDS (36 ml, 17,9 mmol) en THF (70 ml) a -78ºC se le añadió gota a gota 3-metil-3-fenilbutanoato de metilo (3 g, 15,6 mmol) en THF (15 ml). Después de 1 h, se añadió gota a gota trisililazida (5 g, 18,7 mmol) en THF (15 ml) durante 10 min. Después de 5 min más, se añadió ácido acético (4,1 ml) y la mezcla de reacción se calentó a 25ºC durante 1 h. Después, la solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo el compuesto del título (2,6 g, 71%) contaminado con 3-metil-3-fenilbutanoato de metilo al 33% para que se purificara en las siguientes etapas: LCMS (ES) m/e 234 $(M+H)^+$.

b) beta,beta-dimetilfenilalaninato de metilo



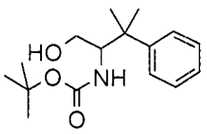
Una solución de 2-azido-3-metil-3-fenilbutanoato de metilo (2,6 g, 11,2 mmol) y PPh_3 (4,4 g, 16,7 mmol) en H_2O (400 µl) y THF (100 ml) se agitó a 25ºC durante 2 d y después a 50ºC durante 12 h. La solución se concentró y se purificó por cromatografía en columna (sílice, MeOH al 5% en DCM (NH_4OH al 1%)), produciendo el compuesto del título (1,4 g, cuant.): LCMS (ES) m/e 208 $(M+H)^+$.

c) 2-amino-3-metil-3-fenil-1-butanol



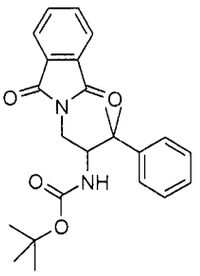
A una solución de beta,beta-dimetilfenilalaninato de metilo (1,4 g, 6,76 mmol) en THF (20 ml) a 0ºC se le añadió gota a gota una solución de hidruro de litio y aluminio (384 mg, 10,1 mmol) en THF (10 ml). Después de calentar a 25ºC durante 12 h, la solución se inactivó mediante la adición secuencial de H_2O (659 µl), NaOH 6 N (500 µl) y H_2O (2,4 ml). El precipitado resultante se filtró y el lecho se lavó minuciosamente con DCM. El filtrado se concentró y se purificó por cromatografía en columna (sílice, MeOH al 2-5% en DCM (NH_4OH al 1%)), produciendo el compuesto del título (770 mg, 64%): LCMS (ES) m/e 179 $(M+H)^+$.

d) [1-(hidroximetil)-2-metil-2-fenilpropil]carbamato de 1,1-dimetiletilo



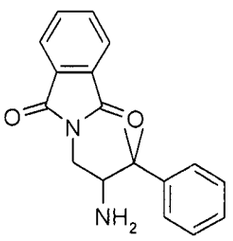
Se añadió en una porción Boc_2O (1 g, 4,76 mmol) a 2-amino-3-metil-3-fenil-1-butanol (770 mg, 4,33 mmol) en THF (20 ml) a 25ºC. Después de 30 min, la solución se concentró, produciendo el compuesto del título (1,2 g, cuant.) en forma de un sólido de color blanco que se usó sin purificación adicional: LCMS (ES) m/e 279 (M+H)+.

e) {1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]-2-metil-2-fenilpropil}carbamato de 1,1-dimetiletilo



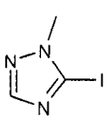
A una solución de [1-(hidroximetil)-2-metil-2-fenilpropil]carbamato de 1,1-dimetiletilo (775 mg, 2,8 mmol), trifenilfosfina (915 mg, 3,5 mmol) y ftalimida (499 mg, 3,4 mmol) en THF (15 ml) a 25ºC se le añadió azodicarboxilato de dietilo (0,54 ml, 3,4 mmol). Después de agitar a TA durante 1 h, se añadió MeOH (5 ml) y la solución se absorbió sobre sílice y se purificó por cromatografía en columna (MeOH al 1% en DCM), produciendo el compuesto del título (723 mg, 64%) en forma de un sólido de color blanco: LCMS (ES) m/z 409 $(M+H)^+$.

f) 2-(2-amino-3-metil-3-fenilbutil)-1*H*-isoindolo-1,3(2*H*)-diona



A una solución de {1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]-2-metil-2-fenilpropil}carbamato de 1,1-dimetiletilo (723 mg, 1,77 mmol) en $CHCl_3$:MeOH (10:1, 55 ml) a TA se le añadió HCl 4 M en dioxano (10 ml). Después de agitar durante 3 h a TA, la solución de reacción se concentró para dar un sólido de color blanco (cuant.): LCMS (ES) m/z 309 $(M+H)^+$.

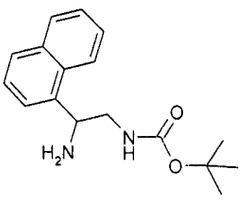
Preparación 15



Preparación de 5-yodo-1-metil-1*H*-1,2,4-triazol

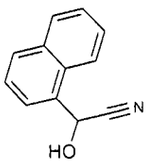
Se añadió lentamente 1-metil-1*H*-1,2,4-triazol (2,05 g, 24,7 mmol) durante 15 minutos a una solución en Et_2O de nBuLi a -70°C. La mezcla se agitó durante 60 minutos a -70°C y se dejó calentar a -30°C. Se añadió lentamente una solución de I_2 (6,5 g, 25,6 mmol) en THF (27 ml) durante 15 minutos y la mezcla se dejó calentar a temperatura ambiente y en agitación durante 60 minutos. La mezcla se repartió con $Na_2S_2O_3$ saturado, las fases se separaron y el disolvente orgánico se retiró. El yoduro bruto se usó sin purificación adicional: LCMS (ES) m/z 210 $(M+H)^+$.

Preparación 16



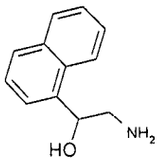
Preparación de [2-amino-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo

a) hidroxi(1-naftalenil)acetonitrilo



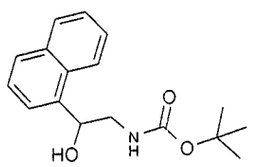
A una solución de cianuro potásico en éter (100 ml) a 0°C se le añadió gota a gota una mezcla de 1-naftalenocarbaldehído (1,56 g, 10 mmol) y ácido acético (1,41 g, 23,5 mmol) en éter (10 ml). La mezcla resultante se calentó a 25°C durante 20 h, momento en el que el precipitado se filtró y el filtrado se concentró, produciendo el compuesto del título en forma de un aceite transparente (1,67 g, 9,14 mmol, 91%): LCMS (ES) m/z 184 $(M+H)^+$.

b) 2-amino-1-(1-naftalenil)etanol



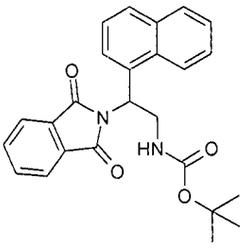
A una solución de hidroxi(1-naftalenil)acetonitrilo (1,67 g, 9,14 mol) en THF (90 ml) a 0°C se le añadió gota a gota una solución de LAH-THF (1 M, 11 ml, 11 mmol). Después de 2 h, la solución se inactivó mediante la adición secuencial de H_2O (0,42 ml), NaOH 6 N (6 M, 0,32 ml) y H_2O (1,6 ml). El precipitado resultante se filtró y el filtrado se concentró y se usó directamente, produciendo el compuesto del título (0,897 g, 4,8 mmol, 53%) en forma de un aceite transparente: LCMS (ES) m/z 188 $(M+H)^+$.

c) [2-hidroxi-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo



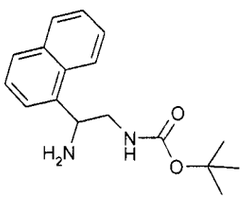
A una solución de 2-amino-1-(1-naftalenil)etanol (1,38 g, 4,8 mmol) en diclorometano (50 ml) se le añadió anhídrido de Boc (1,155 g, 5,3 mmol). Después de agitar a TA durante 12 h, la solución de reacción se concentró y se repartió entre $NaHCO_3$ sat. y DCM. La fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente, produciendo el compuesto del título en forma de un sólido de color blanco (1,378 g, 4,8 mmol, cuant.): LCMS (ES) m/z 288 (M+H)+.

d) [2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo



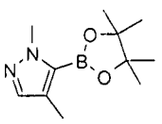
A una solución de [2-hidroxi-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo (1,38 g, 4,8 mmol), trifenilfosfina (1,52 g, 5,76 mmol) y ftalimida (0,74 g, 5,04 mmol) en THF (50 ml) a 25ºC se le añadió azodicarboxilato de dietilo (0,87 ml, 5,52 mmol). Después de agitar a TA durante 1 h, la solución de reacción se concentró al vacío y el residuo se purificó sobre gel de sílice (EtOAc al 20% en hexanos), produciendo el compuesto del título (1,29 g, 3,1 mmol, 65%) en forma de un sólido de color blanco: LCMS (ES) m/z 387 (M+H)+.

e) [2-amino-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo



A una solución de [2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo (1,29 g, 3,1 mmol) en MeOH (30 ml) se le añadió hidrazina anhidra (0,5 ml, 15,5 mmol) a 25ºC. Después de 12 h, la solución se repartió entre DCM y H_2O. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente, produciendo el compuesto del título en forma de un sólido de color blanco (491 mg, 1,72 mmol, 55%): LCMS (ES) m/z 287 $(M+H)^+$.

Preparación 17

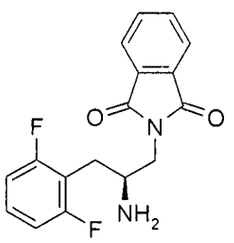


Preparación de 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol

A una suspensión de NaH (al 60% en aceite mineral, 3,5 g, 146 mmol, lavada con 200 ml de hexano) en THF (200 ml) se le añadió gota a gota 4-metil-1H-pirazol (10 g, 122 mmol) a 0°C. Después de agitar a TA durante 1 h, a la suspensión anterior se le añadió gota a gota MeI (7,3 ml, 117 mmol) a 0°C. La mezcla de reacción se agitó durante una noche. El subproducto de NaI se retiró por filtración y la solución del filtrado se usó directamente en la siguiente etapa.

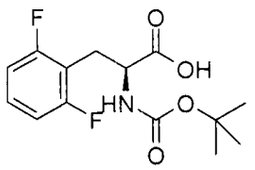
A 0°C, a la solución en THF anterior de 1,4-dimetil pirazol se le añadió n-BuLi (2,5M en hexano, 58,5 ml, 146 mmol). La solución de reacción se agitó durante 2 horas a TA y después se enfrió a -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. A la solución de reacción se le añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (27,2 g, 146 mmol). Después de 15 min a -78°C, la reacción se dejó calentar a 0°C y se agitó durante 3 h. La reacción se diluyó con una solución saturada de NH_4Cl y se extrajo con DCM. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío para producir el compuesto del título en forma de un sólido pardo (21 g, 78%) que se usó directamente sin purificación adicional: LC-MS: 141 $(M-C_6H_{12})^+$, 223 $(M+H)^+$. ^1H RMN ($CDCl_3$): δ 7,28 (s, 1H), 4,03 (s, 3H), 2,22 (s, 3H) y 1,32 (s, 12H).

Preparación 18



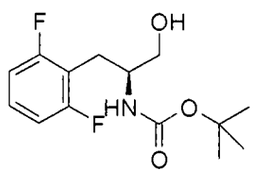
Preparación de 2-[(2*S*)-2-amino-3-(2,6-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona

a) *N*-{[(1,1-dimetiletil)oxi]carbonil}-2,6-difluoro-L-fenilalanina



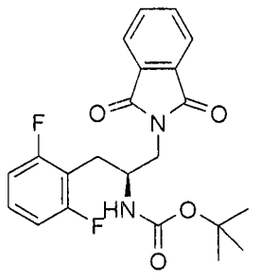
Se añadieron 1,4-dioxano (55 ml) y agua (12 ml) a 2,6-difluoro-L-fenilalanina (3,00 g, 12,62 mmol) en un matraz de fondo redondo de 200 ml. La mezcla se enfrió a 0°C seguido de la adición lenta de NaOH (12,62 ml, 31,6 mmol) y después Boc_2O (3,42 g, 15,20 mmol). La mezcla se dejó calentar a temperatura ambiente y se controló para comprobar que se había completado mediante análisis por LC-MS. Después de que se completara, la mezcla se enfrió a 0°C y se hizo neutra mediante la adición lenta de HCl 2,5 M (12 ml). Los disolventes se retiraron a presión reducida. El sólido resultante se sonicó con MeOH al 20%/$CHCl_3$ (150 ml), se filtró y el disolvente orgánico se retiró para dar el producto (4,3 g, 14,4 mmol, cuant.) en forma de un sólido de color blanco que se usó en la siguiente etapa sin purificación adicional: LC-MS (ES) m/z = 302 $(M+H)^+$.

b) [(1*S*)-2-(2,6-difluorofenil)-1-(hidroximetil)etil]carbamato de 1,1-dimetiletilo



Se añadió lentamente BH_3.THF (64,7 ml, 64,7 mmol) a una solución en tetrahidrofurano (THF) (60 ml) de N-{[(1,1-dimetiletil)oxi]carbonil}-2,6-difluoro-L-fenilalanina (4,33 g, 14,37 mmol) a 0°C en un matraz de fondo redondo de 200 ml. La mezcla se agitó durante 2 horas y después se puso en el congelador durante una noche. El exceso de reactivo se inactivó mediante la adición lenta de AcOH en MeOH a 0°C y la mezcla se calentó a temperatura ambiente durante 2 horas. El volumen de THF se redujo en 1/2 y el producto se repartió entre $CHCl_3$ y $NaHCO_3$ acuoso (sat.). Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se usaron directamente sin purificación adicional (3,4 g, 78%): LC-MS (ES) m/z = 288 $(M+H)^+$.

c) {(1*S*)-2-(2,6-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}carbamato de 1,1-dimetiletilo

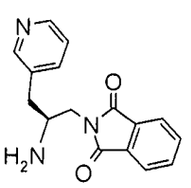


A un matraz de fondo redondo de 200 ml se le añadieron [(1S)-2-(2,6-difluorofenil)-1-(hidroximetil)etil]carbamato de 1,1-dimetiletilo (3,38 g, 11,76 mmol), ftalimida (2,02 g, 13,73 mmol) y PS – TPP (TrifenilFosfina unida a Polímero (2,15 mmol/g, 4,92 g, 14,76 mmol) en tetrahidrofurano (THF) (58,8 ml). Se añadió DEAD (2,23 ml, 14,09 mmol) y la mezcla se agitó a temperatura ambiente durante aproximadamente 30 minutos, momento en el que se añadió MeOH. La mezcla se filtró a través de Celite, se absorbió sobre sílice y se purificó por cromatografía en columna, produciendo el compuesto del título (2,7 g, 55%): LC-MS (ES) m/z = 317 $(M+H)^+$.

d) 2-[(2*S*)-2-amino-3-(2,6-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona

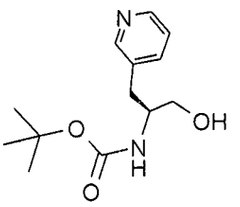
En un matraz de fondo redondo de 200 ml se añadió {(1S)-2-(2,6-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}carbamato de 1,1-dimetiletilo (2,72 g, 6,40 mmol) en cloroformo (75 ml) y metanol (10 ml). Se añadió HCl/1,4-dioxano (40,0 ml, 160 mmol) y la mezcla se agitó durante una noche. Los disolventes se retiraron, produciendo el compuesto del título (2,4 g, cuant.) en forma de la sal HCl: LC-MS (ES) m/z = 317 $(M+H)^+$.

Preparación 19



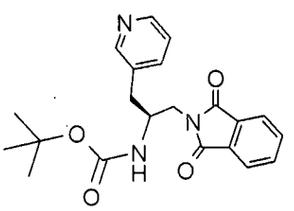
Preparación de 2-[(2*S*)-2-amino-3-(3-piridinil)propil]-1*H*-isoindolo-1,3(2*H*)-diona

a) [(1*S*)-2-hidroxi-1-(3-piridinilmetil)etil]carbamato de 1,1-dimetiletilo



A una solución de Boc-L-3-piridilanilina (1,064 g, 4 mmol) en THF (5 ml) a 0°C se le añadió gota a gota BH_3-THF (20 ml, 20 mmol-1 M en THF). Después de 2 h, la reacción se interrumpió con AcOH:MeOH (1:5, 14,3 ml) a 0°C, seguido de Et_3N (1,67 ml, 12 mmol) e I_2 (2,03 g, 8 mmol). La mezcla resultante se calentó a temperatura ambiente y se agitó durante 20 h, cambiando de color pardo a incoloro. La solución se concentró y se repartió entre DCM y agua. Después, la fase acuosa se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron para producir el producto deseado en forma de un aceite incoloro que se usó sin purificación adicional (957,6 mg, 95%): LC-MS (ES) m/z = 253 $(M+H)^+$.

b) [(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-(3-piridinilmetil)etil]carbamato de 1,1-dimetiletilo

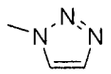


A una solución de [(1*S*)-2-hidroxi-1-(3-piridinilmetil)etil]carbamato de 1,1-dimetiletilo (958 mg, 3,8 mmol), trifenilfosfina (1,21 g, 4,6 mmol) y ftalimida (617 mg, 4,2 mmol) en THF (40 ml) a 25°C se le añadió azodicarboxilato de dietilo (0,72 ml, 4,6 mmol). Después de agitar a TA durante 1 h, la solución de reacción se concentró al vacío y el residuo se purificó sobre gel de sílice (acetato de etilo al 0-50%/hexano), produciendo el compuesto del título (797 mg, 55%) en forma de un sólido de color blanco: LCMS (ES) m/z 382 $(M+H)^+$.

c) 2-[(2*S*)-2-amino-3-(3-piridinil)propil]-1*H*-isoindolo-1,3(2*H*)-diona

A una solución de [(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-(3-piridinilmetil)etil]carbamato de 1,1-dimetiletilo (796,7 mg, 2,1 mmol) en DCM (10 ml) a TA se le añadió HCl 1 M en dioxano (10 ml). Después de 20 h, la solución se concentró, produciendo el compuesto del título (404 mg, 68%) en forma de la sal HCl: LCMS (ES) m/z 282 $(M+H)^+$.

Preparación 20

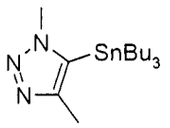


Preparación de 1-metil-1*H*-1,2,3-triazol

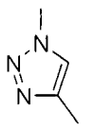
A una solución de 1,2,3-trazol (10 g, 145 mmol) en 150 ml de THF se le añadieron carbonato potásico (40 g, 290 mmol) y MeI (13,58 ml, 217 mmol). La mezcla de reacción resultante se agitó a ta durante 3 h. La mezcla de reacción se filtró y el filtrado se concentró para producir el compuesto del título (9,2 g, 78%). ^{1}H RMN (400 MHz, $CDCl_3$) ppm 7,71 (s, 1H), 7,55 (s, 1H), 4,14 (s, 3H).

Preparación 21

Preparación de 1,4-dimetil-5-(tributilestannanil)-1*H*-1,2,3-triazol



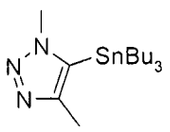
a) 1,4-dimetil-1*H*-1,2,3-triazol



Una solución de metilamina (25,4 ml, 50,8 mmol, 2 M en MeOH) se añadió gota a gota a una suspensión de N'-(2,2-dicloro-1-metiletilideno)-4-metilbencenosulfonohidrazida (ref: Sakai, K. et al, *Bull. Chem. Soc. Jpn.*, **1986**, *59*,

179-183) (3 g, 10,16 mmol) en metanol (10 ml) a 0°C. El sólido se disolvió. La mezcla parda oscura resultante se agitó a 0°C durante 2 h, se evaporó y el sólido se filtró y se aclaró con EtOAc. Los filtrados combinados se concentraron y se purificaron sobre una columna biotage 25 M, que se eluyó con 50-75% de AE/hexano para dar 0,57 g de un líquido pardo. LC-MS (ES) m/z = 98 $(M+H)^+$, ^1H RMN ($CDCl_3$, 400 MHz) 7,27 (s, 1H), 4,06 (s, 3H), 2,35 (s, 3H).

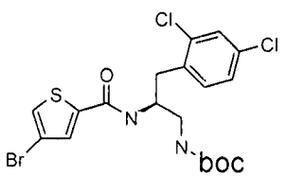
b) 1,4-dimetil-5-(tributilestannanil)-1*H*-1,2,3-triazol



Una solución de 1,4-dimetil-1,2,3-triazol (0,56 g, 5,77 mmol) en THF (5 ml) se añadió gota a gota a una solución de BuLi (2,77 ml, 6,92 mmol, 2,5 M en hexano) en 30 ml de THF a -78°C en una atmósfera de N_2. La mezcla turbia resultante se agitó a -70°C durante 1 h.

Después, se añadió cloruro de tributilestaño (1,711 ml, 6,34 mmol). La mezcla de reacción se hizo transparente, se agitó a esta temperatura durante 30 min y se calentó gradualmente a ta. A la mezcla de reacción se le añadieron 10 ml de NH_4Cl y 10 ml de agua. La mezcla de reacción se extrajo con éter. Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron. El residuo se purificó sobre FCC (AE al 20%/Hexano) para dar 1,7 g de un líquido transparente (73%). LC-MS (ES) m/z = 388 $(M+H)^+$, ^1H RMN ($CDCl_3$, 400 MHz) 4,05 (s, 3H), 2,38 (s, 3H), 1,5-0,9 (m, 27H)

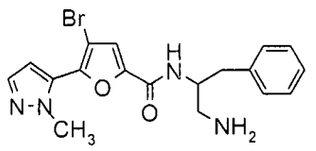
Preparación 22



Preparación de [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(2,4-diclorofenil)propil]carbamato de 1,1-dimetiletilo

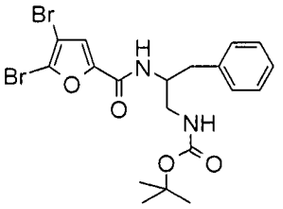
Una solución de ácido 4-bromo-2-tiofenocarboxílico (1,29 g, 6,22 mmol), 2-[(2*S*)-2-amino-3-(2,4-diclorofenil)propil]-1H-isoindolo-1,3(2H)-diona (2,0 g, 5,19 mmol), PyBrop (3,62 g, 7,78 mmol) y Base de Hunig (3,62 ml, 20,74 mmol) en DCM (50 ml) se agitó a TA durante 30 min. La mezcla de reacción se lavó con H_2O, HCl 1 N, $NaHCO_3$ (ac. sat.) y salmuera. El disolvente se retiró y el residuo se disolvió en MeOH y se le añadió gota a gota hidrazina monohidrato (1,3 g, 26 mmol). La reacción se agitó a ta durante una noche. Se formó un sólido blanco, se filtró y se aclaró con DCM. A los filtrados se les añadieron $(Boc)_2O$ (1,7 g, 7,78 mmol) y $NaHCO_3$ (ac. sat., 3 ml). La mezcla de reacción se agitó a TA durante 2 horas y se lavó con $NaHCO_3$ (ac. sat.) y salmuera. El disolvente se retiró y el residuo se purificó por biotage (H al 50%/E) para dar el producto (2,0 g, 76%). LC-MS (ES) m/z = 531,0 $(M+Na)^+$.

Ejemplo 1



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

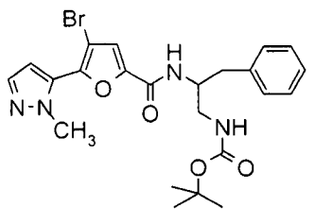
a) (2-{[(4,5-dibromo-2-furanil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo



A una solución de ácido 4,5-dibromo-2-furanocarboxílico (2,81 g, 10,4 mmol), PyBrOP (5,6 g, 12,0 mmol) y diisopropiletil amina (4,2 ml, 24,0 mmol) en DCM (70 ml) a 25°C se le añadió (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (2,0 g, 8,0 mmol). Después de 16 h, la solución se repartió entre H_2O y se lavó con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se

concentraron y se purificaron por cromatografía en columna (sílice, hexanos/EtOAc, 2:1), produciendo el compuesto del título (4,3 g, 82%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 503 $(M+H)^+$.

b) [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo

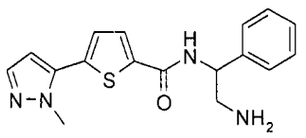


A una solución de (2-{[(4,5-dibromo-2-furanil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (0,30 g, 0,60 mmol) en dioxano/H_2O (5:1, 8,6 ml) se le añadieron K_2CO_3 (0,25 g, 1,8 mmol), tetraquistrifenilfosfina Pd(0) (70 mg, 0,06 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (0,12 g, 0,60 mmol). La mezcla de reacción se calentó a 88ºC en un tubo cerrado herméticamente durante 12 h. La solución de reacción se vertió en H_2O (100 ml) y se extrajo con DCM. Los extractos orgánicos se secaron (Na_2SO_4), se concentraron al vacío y se purificaron sobre gel de sílice (hexanos/EtOAc, 1:1) para dar el compuesto del título (0,20 g, 66%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 504.

c) *N*-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

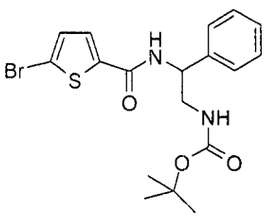
Se disolvió [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (0,20 g, 0,40 mmol) en DCM (10 ml) y la mezcla se trató con TFA (5 ml). Después de 2 h, la solución se concentró y se purificó sobre HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%), produciendo la sal TFA del compuesto del título (0,16 g, 91%) en forma de un polvo de color blanco: LC-MS (ES) m/z = 405 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 7,59 (s, 1H), 7,33 (m, 3H), 7,30 (m, 2H), 6,85 (s, 1H), 4,57 (m, 1H), 4,03 (s, 3H), 3,25 (m, 1H), 3,14 (m, 1H) y 2,98 (m, 2H).

Ejemplo 2:



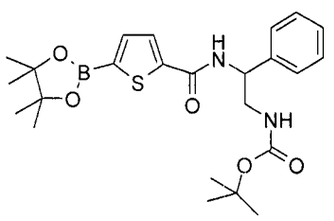
Preparación de *N*-(2-amino-1-feniletil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) (2-{[(5-bromo-2-tienil)carbonil]amino}-2-feniletil)carbamato de 1,1-dimetiletilo



A una solución de ácido 5-bromo-2-tiofenocarboxílico (3,2 g, 15,2 mmol), PyBrOP (8,5 g, 18,2 mmol) y diisopropiletil amina (10,6 ml, 60,9 mmol) en DCM (76 ml) a 25°C se le añadió (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo (3,6 g, 3,14 mmol) [preparado en la Preparación 1]. Después de 16 h, la solución se repartió entre H_2O y se lavó con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en columna (sílice, MeOH al 1% en DCM), produciendo el compuesto del título (4 g, 62%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 426 $(M+H)^+$.

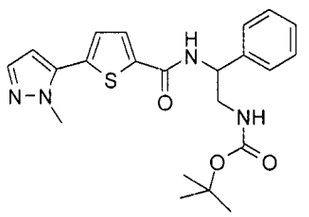
b) [2-fenil-2-({[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-tienil]carbonil}amino)etil]carbamato de 1,1-dimetiletilo



A una solución de (2-{[(5-bromo-2-tienil)carbonil]amino}-2-feniletil)carbamato de 1,1-dimetiletilo (1 g, 2,35 mmol) en DMF (9 ml) se le añadieron KOAc (693 mg,

7,05 mmol), bis(pinocolato)diboro (1,2 g, 4,71 mmol) y $Pd(dppf)Cl_2$ (169 mg, 0,212 mmol). Los contenidos de la reacción se calentaron a 80°C en un tubo cerrado herméticamente durante 18 horas y después se repartieron entre NaOH 6 N y DCM. El valor del pH de la fracción acuosa se ajustó a ~3 con HCl 3 M y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron al vacío para dar un sólido y se usaron directamente en la siguiente reacción: LC-MS (ES) m/z = 473 $(M+H)^+$ éster borónico, 391 $(M+H)^+$ ácido borónico.

c) [2-({[5-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo



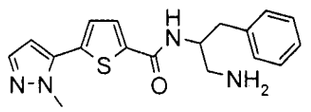
A una solución de [2-fenil-2-({[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-tienil]carbonil}amino)etil]carbamato de 1,1-dimetiletilo (200 mg, 0,42 mmol) en dioxano/H_2O (5:1, 8,6 ml) se le añadieron K_2CO_3 (234 mg, 1,69 mmol), tetraquistrifenilfosfina Pd(0) (24 mg, 0,02 mmol) y 5-yodo-1-metil-1H-pirazol (97 mg, 0,47 mmol) [preparada de acuerdo con Effenberger, F.; et al *J. Org. Chem.* **1984**, 49, 24, 4687]. La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 12 h. La solución de reacción se vertió en H_2O (100 ml) y se extrajo con DCM. Los extractos orgánicos se secaron (Na_2SO_4), se concentraron al vacío y se purificaron sobre gel de sílice (MeOH al 1% en DCM) para dar el compuesto del título (56 mg, 31%) en forma de un sólido de color amarillo: LC-MS (ES) m/z = 427.

d) *N*-(2-amino-1-feniletil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

Se disolvió [2-({[5-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo (56 mg, 0,131 mmol) en MeOH (2 ml) y la mezcla se trató con un exceso de HCl 4 M en dioxano (656 µl, 2,62 mmol). Después de 4 h, la solución se concentró, produciendo el compuesto del título (46

mg, cuant.) en forma de un sólido de color amarillo: LC-MS (ES) m/z 327 $(M+H)^+$, ^1H RMN (d6-DMSO, 400 MHz) 9,46 (d, J = 8,2 Hz, 1H), 8,27 (s a, 1H), 8,20 (d, J = 4,0 Hz, 1H), 7,48-7,75 (m, 3H), 7,37-7,40 (m, 2H), 7,31-7,33 (m, 1H), 6,58 (d, J = 1,9 Hz, 1H), 5,21-5,30 (m, 1H), 3,97 (s, 3H), 3,36-3,41 (m, 1H), 3,19-3,25 (m, 1H).

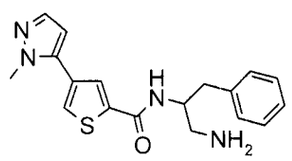
Ejemplo 3



Preparación de N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color castaño de acuerdo con el Ejemplo 2, con la excepción de que se sustituyó (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo por (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (1,65 g, 7,97 mmol) [preparado en la Preparación 2]: LC-MS (ES) m/z 341 $(M+H)^+$, ^1H RMN (d_6-DMSO, 400 MHz) 8,74 (d, J = 8,5 Hz, 1H), 8,05 (s a, 1H), 7,89 (d, J = 3,9 Hz, 1H), 7,47 (d, J = 1,9 Hz, 1H), 7,43 (d, J = 3,9 Hz, 1H), 7,26-7,29 (m, 3H), 7,20-7,22 (m, 1H), 6,56 (d, J = 2,0 Hz, 1H), 4,31-4,42 (m, 1H), 2,98-3,01 (m, 2H), 2,91-2,93 (m, 2H).

Ejemplo 4

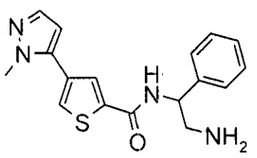


Preparación de N-[2-amino-1-(fenilmetil)etil]-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 2, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (1 g, 4,83 mmol) y (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo por (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (1,2 g, 4,83 mmol) [preparado en la Preparación 2]: LC-MS (ES)

m/z 441 $(M+H)^+$, ^1H RMN (d6-DMSO, 400 MHz) 8,98 (s a, 1H), 8,29 (s, 1H), 8,17 (s a, 2H), 7,98 (s, 1H), 7,46 (s, 1H), 7,27-7,29 (m, 3H), 7,19 (s, 1H), 6,46 (s, 1H), 4,35-4,37 (m, 1H), 3,51 (s, 3H), 2,75-3,12 (m, 4H).

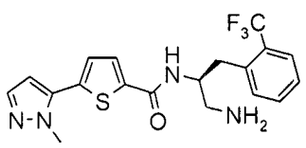
Ejemplo 5



Preparación de N-(2-amino-1-feniletil)-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida

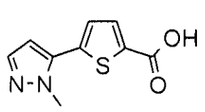
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 2, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (650 mg, 3,14 mmol): LC-MS (ES) m/z 427 $(M+H)^+$, ^1H RMN (d6-DMSO, 400 MHz) 9,65 (d, J = 7,3 Hz, 1H), 8,58 (s, 1H), 8,31 (s a, 2H), 7,99 (s, 1H), 7,42-7,51 (m, 2H), 7,72-7,80 (m, 2H), 7,20-7,31 (m, 1H), 6,51 (s, 1H), 3,52 (s, 1H), 5,25-5,35 (m, 1H), 3,51 (s, 3H), 3,32-3,48 (m, 1H), 3,15-3,21 (m, 1H).

Ejemplo 6:



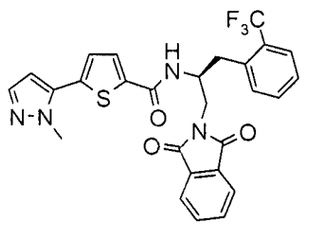
Preparación de N-(2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



A una solución de ácido 5-bromo-2-tiofenocarboxílico (100 mg, 0,48 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (267 mg, 1,93 mmol), tetraquistrifenilfosfina Pd(0) (28 mg, 24 μmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (94 mg, 0,48 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 12 h y después se repartió entre NaOH 6 N y DCM. El valor del pH de la fase acuosa se ajustó a ~3 con HCl 3 M y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional (~100 mg, cuant.): LC-MS (ES) m/z = 209 $(M+H)^+$.

b) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (100 mg, 0,48 mmol), PyBrOP (270 mg, 0,58 mmol) y diisopropiletil amina (420 μl, 2,4 mmol) en DCM (5 ml) a 25°C se le añadió 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl (168 mg, 0,48 mmol) [de la Preparación 6]. Después de 16 h, la solución se repartió entre H_2O y se lavó con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en columna (sílice), produciendo el compuesto del título (74 mg, 28%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 539 $(M+H)^+$.

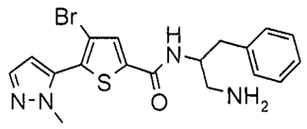
c) N-(2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (74 mg, 0,14 mmol) en MeOH/THF (2 ml, 1:1) a TA se le añadió hidrazina (86 μl, 2,75 mmol). Después de agitar durante 18 h a TA, la solución de reacción se concentró

al vacío y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título.

El compuesto neutro anterior se disolvió en MeOH (2 ml), se trató con un exceso de HCl 4 M en dioxano (500 l) y se concentró, produciendo la sal HCl del compuesto del título: LC-MS (ES) m/z = 409 $(M+H)^+$, ^1H RMN (d6-DMSO, 400 MHz) 8,97 (d, J = 9,0 Hz, 1H), 8,17 (s a, 1H), 8,00 (d, 3,8 Hz, 1H), 7,68 (d, J = 7,8 Hz, 1H), 7,55-7,61 (m, 2H), 7,42-7,47 (m, 2H), 6,56 (d, J = 2,0 Hz, 1H), 4,47-4,51 (m, 1H), 4,18 (s, 3H), 3,09-3,11 (m, 4H).

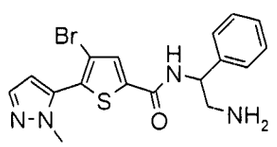
Ejemplo 7



Preparación de N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 1, con la excepción de que se sustituyó ácido 4,5-dibromofuranocarboxílico por ácido 4,5-dibromotiofenocarboxílico (376 mg, 1,32 mmol): LC-MS (ES) m/z = 419 $(M+H)^+$, ^1H RMN (d6-DMSO, 400 MHz) 8,92 (d, J = 8,6 Hz, 1H), 8,03-8,06 (m, 2H), 7,56 (d, J = 1,9 Hz, 1H), 7,26-7,32 (m, 3H), 7,21-7,23 (m, 1H), 6,55 (d, J = 1,9 Hz, 1H), 4,32-4,42 (m, 1H), 3,77 (s, 3H), 3,00-3,01 (m, 2H), 2,89-2,91 (m, 2H).

Ejemplo 8

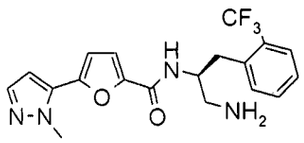


Preparación de N-(2-amino-1-feniletil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 1, con la excepción de que se sustituyó ácido 4,5-

dibromofuranocarboxílico por ácido 4,5-dibromotiofenocarboxílico (2,2 g, 7,69 mmol) y (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo por (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo (1,1 g, 4,66 mmol): LC-MS (ES) m/z = 406 $(M+H)^+$, ^1H RMN (d6-DMSO, 400 MHz) 9,47 (d, J = 7,9 Hz, 1H), 8,26 (s, 1H), 8,17 (s a, 1H), 7,58 (d, J = 1,6 Hz, 1H), 7,38-7,46 (m, 3H), 7,30-7,34 (m, 1H), 6,56 (d, J = 1,6 Hz, 1H), 5,28-5,37 (m, 1H), 3,81 (s, 3H), 3,35-3,41 (m, 1H), 3,21-3,28 (m, 1H).

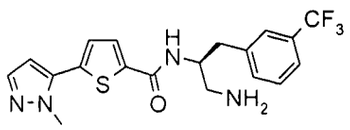
Ejemplo 9



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 5-bromo-2-furanocarboxílico (58 mg, 0,3 mmol): LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 7,62 (s a, 1H), 7,57 (m, 1H), 7,51 (m, 3H), 7,22 (m, 1H), 6,91 (m, 1H), 6,76 (m, 1H), 4,6 (m, 1H), 4,07 (m, 3H) y 3,15 (m, 4H).

Ejemplo 10:

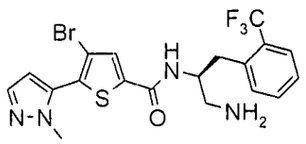


Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-

diona-HCl (306 mg, 0,80 mmol): LC-MS (ES) m/z = 409 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) ppm 2,81 - 2,88 (m, 1H) 2,93 (td, *J* = 9,03, 4,93 Hz, 2H) 3,09 (dd, *J* = 13,89, 5,31 Hz, 1H) 4,00 (s, 3H) 4,28 - 4,35 (m, 1H) 6,53 (d, *J* = 2,02 Hz, 1 H) 7,32 (d, *J* = 4,04 Hz, 1H) 7,45 - 7,52 (m, 3H) 7,54 - 7,58 (m, 1H) 7,60 (s, 1H) 7,70 (d, *J* = 4,04 Hz, 1H).

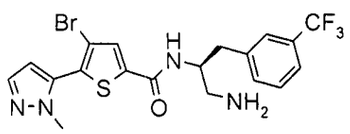
Ejemplo 11



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (237 mg, 0,83 mmol): LC-MS (ES) m/z = 488 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2,97 - 3,10 (m, 4H) 3,78 (s, 3H) 4,42 - 4,54 (m, 1H) 6,56 (d, *J* = 2,02 Hz, 1H) 7,45 (t, *J* = 7,58 Hz, 1H) 7,50 - 7,54 (m, 1H) 7,56 - 7,63 (m, 2H) 7,71 (d, *J* = 7,58 Hz, 1H) 7,92 (s, 1H) 8,76 (d, *J* = 9,09 Hz, 1H)

Ejemplo 12

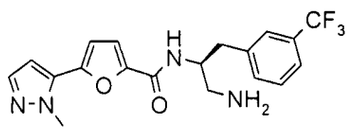


Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (237 mg, 0,83 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-

isoindolo-1,3(2H)-diona-HCl por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl (206 mg, 0,535 mmol): LC-MS (ES) m/z = 488 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) ppm 2,97 - 3,07 (m, 1H) 3,10 - 3,21 (m, 2H) 3,27 (d, *J* = 3,54 Hz, 1H) 3,82 (s, 3H) 4,50 - 4,59 (m, 1H) 6,51 (d, *J* = 2,02 Hz, 1H) 7,50 - 7,60 (m, 4H) 7,62 (s, 1H) 7,71 (s, 1H).

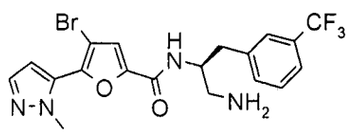
Ejemplo 13:



Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 5-bromo-2-furanocarboxílico (44 mg, 0,23 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl (87 mg, 0,25 mmol): LC-MS (ES) m/z = 393 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 7,63 (s a, 1H), 7,57 (m, 1H), 7,51 (m, 3H), 7,22 (m, 1H), 6,91 (m, 1H), 6,77 (m, 1H), 4,6 (m, 1H), 4,07 (m, 3H) y 3,14 (m, 4H).

Ejemplo 14:

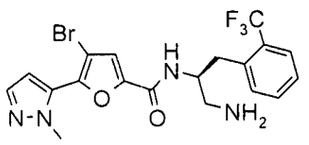


Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-furanocarboxílico (82

mg, 0,3 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl (115 mg, 0,3 mmol): LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 7,61 (m, 2H), 7,53 (m, 3H), 7,30 (m, 1H), 6,84 (m, 1H), 4,59 (m, 1H), 4,03 (s, 3H), 3,28 (m, 1H), 3,17 (m, 2H) y 3,01 (m, 1H)

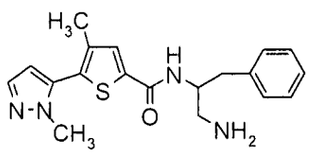
Ejemplo 15



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

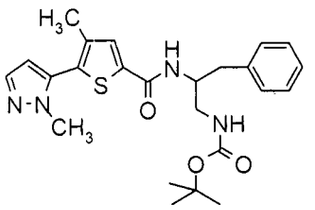
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-furanocarboxílico (82 mg, 0,3 mmol): LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 7,71 (m, 1H), 7,60 (m, 1H), 7,53 (m, 2H), 7,44 (m, 1H), 7,33 (m, 1H), 6,88 (m, 1H), 4,7 (m, 1H), 4,06 (s, 3H), 3,25 (m, 3H) y 3,09 (m, 1H).

Ejemplo 16



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) [2-({[4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo

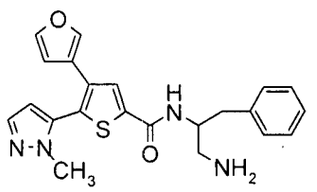


A una solución de [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (0,35 g, 0,67 mmol) [del Ejemplo 7] en dioxano/H_2O (5:1, 25:5 ml) se le añadieron K_2CO_3 (0,28 mg, 2,0 mmol), tetraquistrifenilfosfina Pd(0) (77 mg, 0,06 mmol) y trimetilboroxina (0,17 ml, 1,2 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 12 h. La solución de reacción se concentró al vacío y se purificó sobre gel de sílice (hexanos/EtOAc, 1:1) para dar el compuesto del título (0,10 g, 33%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 455 $(M+H)^+$.

b) *N*-[2-amino-1-(fenilmetil)etil]-4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

Se disolvió [2-({[4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (0,10 g, 0,22 mmol) en MeOH (10 ml) y THF (5 ml) y la mezcla se trató con HCl 4 M en dioxano (5 ml). Después de 4 h, la solución se concentró, produciendo la sal HCl del compuesto del título (68 mg, 91%) en forma de un polvo de color blanco: LC-MS (ES) m/z = 355 $(M+H)^+$, ^{1}H RMN (d_4-MeOH, 400 MHz) 7,79 (s, 1H), 7,68 (s, 1H), 7,31 (m, 4H), 7,25 (m, 1H), 6,56 (s, 1H), 4,54 (m, 1H), 3,87 (s, 3H), 3,69 (s, 2H), 3,34 (m, 2H), 3,03 (d, J = 7,6 Hz, 2H) y 2,21 (s, 3H).

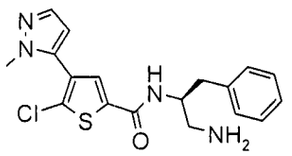
Ejemplo 17



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-(3-furanil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

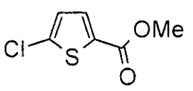
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 16, con la excepción de que se sustituyó trimetilboroxina por ácido 3-furanoborónico (0,13 g, 1,2 mmol): LC-MS (ES) m/z = 472 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 8,13 (s, 1H), 7,81 (s, 1H), 7,53 (m, 2H), 7,34 (m, 4H), 7,26 (m, 1H), 6,61 (s, 1H), 6,20 (s, 1H), 4,57 (m, 1H), 3,68 (s, 2H), 3,63 (s, 3H), 3,24 (m, 2H) y 3,07 (m, 2H)

Ejemplo 18



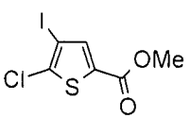
Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-2-tiofenocarboxilato de metilo



A una solución de ácido 5-cloro-2-tiofenocarboxílico (2,0 g, 12,3 mmol) en MeOH seco (75 ml) se le añadió H_2SO_4 (1 ml). La mezcla de reacción se calentó a 58°C durante 20 h y después se concentró al vacío. El residuo se disolvió en DCM y se lavó varias veces con una solución saturada d NaHCO3. La fracción orgánica se secó (Na_2SO_4), se concentró al vacío y se usó directamente sin purificación adicional (21,3 g, cuant.): LC-MS (ES) m/z = 177 $(M+H)^+$.

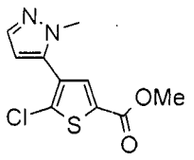
b) 5-cloro-4-yodo-2-tiofenocarboxilato de metilo



A una solución de ácido 5-cloro-2-tiofenocarboxílico (5,0 g, 28,0 mmol) en ácido acético (150 ml) se le añadieron $ZnCl_2$ (38 g, 280 mmol) y dicloroyodato de

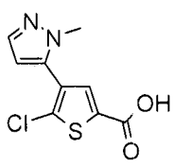
benciltrimetilamonio (20,5 g, 58,8 mmol) [*Bull. Chem. Soc. Jpn.* **64**, 2566-2568 (1991)]. La mezcla de reacción se calentó a 78ºC durante 48 h y después se concentró al vacío. El residuo se extrajo con hexanos (2 x 200 ml) y la solución de hexano se lavó con una solución saturada de $NaHCO_3$. Las fracciones orgánicas se secaron (Na_2SO_4), se concentraron al vacío y se purificaron sobre gel de sílice (hexanos/EtOAc, 4:1) para dar el compuesto del título (3,8 g, 45%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z = 302 $(M+H)^+$.

c) 5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



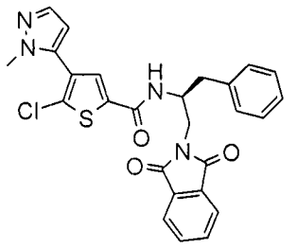
A una solución de 5-cloro-4-yodo-2-tiofenocarboxilato de metilo (1,75 g, 5,8 mmol) en dioxano/H_2O (50:5 ml) se le añadieron K_2CO_3 (3,4 g, 24,9 mmol), tetraquistrifenilfosfina Pd(0) (0,96 g, 0,83 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (3,4 g, 16,5 mmol). La mezcla de reacción se calentó a 88ºC en un tubo cerrado herméticamente durante 15 h. La solución de reacción se concentró al vacío y se purificó sobre gel de sílice (hexanos/EtOAc, 4:1) para dar el compuesto del título (0,35 g, 24%) en forma de un aceite de color amarillo: LC-MS (ES) m/z = 257 $(M+H)^+$.

d) ácido 5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A una solución de 5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (0,30 g, 1,17 mmol) en THF (10 ml) y MeOH (10 ml) se le añadió NaOH 6 N (5 ml). La solución de reacción se calentó a 50ºC durante 2 h. La solución de reacción se concentró al vacío, se hizo ácida (pH ~ 2) con HCl 3 N y se extrajo con DCM. La solución orgánica se secó (Na_2SO_4) y se concentró para dar un sólido (0,22 g) que se usó sin purificación adicional. LC-MS (ES) m/z = 243 $(M+H)^+$.

e) 5-cloro-*N*-[(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-(fenilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



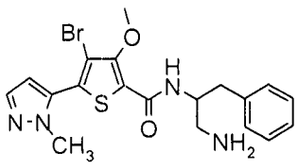
A una solución de ácido 5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (0,21 g, 0,87 mmol), PyBrOP (610 mg, 1,3 mmol) y diisopropiletil amina (0,76 ml, 4,35 mmol) en DCM (20 ml) a 25ºC se le añadió 2-[(2*S*)-2-amino-3-fenilpropil]-1*H*-isoindolo-1,3(2*H*)-diona·HCl (380 mg, 0,96 mmol) [preparada de acuerdo con la Preparación 5]. Después de 16 h, la solución se repartió entre H_2O y se lavó con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en columna (sílice), produciendo el compuesto del título (200 mg, 46%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 505 $(M+H)^+$.

f) *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A una solución de 5-cloro-*N*-[(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-(fenilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (200 mg, 0,40 mmol) en MeOH/THF (10 ml, 1:1) a TA se le añadió hidrazina hidrato (0,20 ml, 4,0 mmol). Después de agitar durante 24h a TA, la solución de reacción se concentró al vacío y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título en forma de un sólido de color amarillo claro.

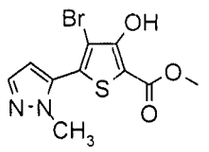
El compuesto neutro de la etapa anterior se disolvió en DCM (2 ml), se trató con un exceso de HCl 4 M en dioxano (1 ml) y se concentró, produciendo la sal HCl (102 mg) del compuesto del título: LC-MS (ES) m/z = 375 $(M+H)^+$, 7,78 (s, 1H), 7,63 (s, 1H), 7,31 (m, 4H), 7,26 (m, 1H), 6,55 (s, 1H), 4,54 (m, 1H), 3,91 (s, 3H), 3,24 (m, 2H) y 3,03 (m, 2H).

Ejemplo 19



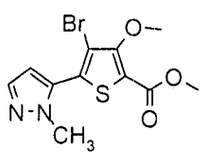
Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 4-bromo-3-hidroxi-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Se combinaron 4,5-dibromo-3-hidroxi-2-tiofenocarboxilato de metilo (500 mg, 1,59 mmol), 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (339 mg, 1,75 mmol), $Pd(PPh_3)_4$ (92 mg, 79,4 μmol) y K_2CO_3 (876 mg, 6,35 mmol) en dioxano (6,6 ml) y H_2O (1,3 ml) en un tubo cerrado herméticamente. Después de 12 h a 80°C, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, MeOH al 0,5% en DCM), produciendo el compuesto del título (75 mg, 15%) en forma de un residuo pardo: LCMS (ES) m/z = 318 $(M+H)^+$.

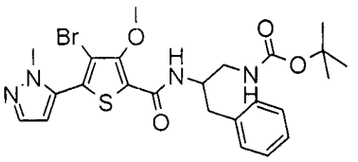
b) 4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 4-bromo-3-hidroxi-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (175 mg, 0,554 mmol), MeOH (26 μl, 0,609 mmol) y PPh_3 (189 mg, 0,720 mmol) en THF (6 ml) a 25°C se le añadió en una porción

DEAD (113 µl, 0,720 mmol). Después de 30 min, la reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo el compuesto del título (135 mg, 74%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 332 $(M+H)^+$.

c) [2-({[4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



i) Una solución de 4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (135 mg, 0,410 mmol) en NaOH 6 N (4 ml) y THF (4 ml) se agitó en un tubo cerrado herméticamente a 80°C. Después de 2 h, la solución se acidificó a un valor de pH de 3 usando HCl 1 N y después se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z = 318 $(M+H)^+$.

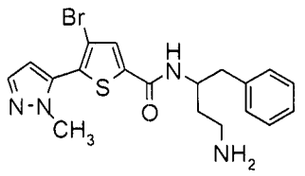
ii) A una solución del ácido bruto, (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (88 mg, 0,351 mmol) [de la Preparación 2] y diisopropiletil amina (305 µl, 1,76 mmol) en DCM (3,5 ml) se le añadió en una porción PyBrop (196 mg, 0,422 mmol). Después de 12 h, se añadieron más cantidad de diisopropiletil amina (305 µl, 1,76 mmol) y PyBrop (196 mg, 0,422 mmol). Después de 2 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z = 550 $(M+H)^+$.

d) N-[2-amino-1-(fenilmetil)etil]-4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

Una solución de [2-({[4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (en bruto, de la parte e) en TFA-DCM (3 ml, 1:2) se agitó a 25°C. Después de 30 min, la solución se concentró y el residuo se neutralizó a través de un lecho de sílice (MeOH al 3% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

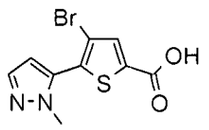
Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título en forma de la sal HCl: LC-MS (ES) m/z 450 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,07 (s a, 3 H) 7,85 (d, J = 8,84 Hz, 1 H) 7,58 (d, J = 2,02 Hz, 1 H) 7,32 (d, J = 7,07 Hz, 2 H) 7,26 - 7,29 (m, 2 H) 7,20 - 7,24 (m, 1 H) 6,54 (d, J = 2,02 Hz, 1 H) 4,50-4,55 (m, 1H) 3,79 (d, J = 6,82 Hz, 3 H) 3,74 (d, J = 6,57 Hz, 1 H) 3,17 (s, 1 H) 2,98-3,10 (m, 4 H).

Ejemplo 20:



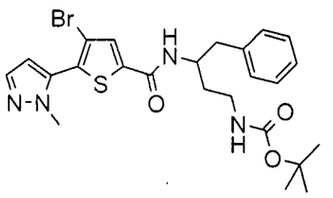
Preparación de *N*-[3-amino-1-(fenilmetil)propil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



A una solución de ácido 4,5-dibromo-2-tiofenocarboxílico (1 g, 3,5 mmol) en dioxano/H_2O (5:1, 18 ml) se le añadieron K_2CO_3 (1,9 g, 13,98 mmol), tetraquistrifenilfosfina Pd(0) (201 mg, 0,175 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (678 mg, 3,5 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 12 h y después se repartió entre NaOH 6 N y DCM. El valor del pH de la fase acuosa se ajustó a ~3 con HCl 3 M y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional (~1 g, cuant.): LC-MS (ES) m/z = 288 $(M+H)^+$.

b) [3-({[4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-4-fenilbutil]carbamato de 1,1-dimetiletilo



A una solución de ácido 4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (250 mg, 0,874 mmol), PyBrOP (489 mg, 8,74 mmol) y diisopropiletil amina (762 µl, 4,37 mmol) en DCM (8 ml) a 25ºC se le añadió (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo (230 mg, 0,874 mmol) [preparado de acuerdo con la Preparación 8]. Después de 16 h, la solución se repartió entre H_2O y se lavó con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en columna (sílice), produciendo el compuesto del título (130 mg, 29%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 533 $(M+H)^+$.

c) N-[3-amino-1-(fenilmetil)propil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

Una solución de [3-({[4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-4-fenilbutil]carbamato de 1,1-dimetiletilo (130 mg, 0,24 mmol) en TFA-DCM (3 ml, 1:2) se agitó a 25ºC. Después de 30 min, la solución se concentró y el residuo se neutralizó a través de un lecho de sílice (MeOH al 3% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (40 mg, 40%) en forma de la sal HCl: LC-MS (ES) m/z 433 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,68 (d, J = 8,59 Hz, 1 H) 7,97 (s, 1 H) 7,77 (s a, 3 H) 7,57 (d, J = 2,02 Hz, 1 H) 7,28 (d, J = 2,27 Hz, 3 H) 7,25 - 7,32 (m, 2 H) 6,55 (d, J = 2,02 Hz, 1 H) 4,17 - 4,24 (m, 1 H) 3,78 (s, 3 H) 2,77 - 2,89 (m, 4 H) 1,85 - 1,92 (m, 1 H) 1,81 (td, J = 9,54, 4,93 Hz, 1 H).

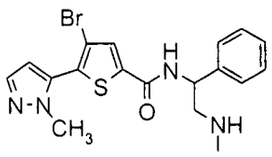
Ejemplo 21

Organizacion y
Digitalizacion CSA Ltda.

PATENTE DE INVENCIÓN

09-82387

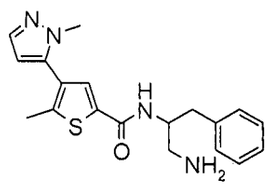
4/5



Preparación de 4-bromo-N-[2-(metilamino)-1-feniletil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se sustituyó (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo por (2-amino-2-feniletil)metilcarbamato de 1,1-dimetiletilo (1 g, 4,02 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1] y se sustituyó ácido 4,5-dibromo-2-furanocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (1,89 g, 6,6 mmol): LCMS (ES) m/z 420 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 9,64 (d, J = 8,34 Hz, 1 H) 8,91 (s a, 1 H) 8,33 (s, 1 H) 7,58 (d, J = 2,02 Hz, 1 H) 7,42 - 7,50 (m, 2 H) 7,38 - 7,42 (m, 2 H) 7,34 (d, J = 7,07 Hz, 1 H) 6,56 (d, J = 2,02 Hz, 1 H) 5,37 - 5,44 (m, 1 H) 3,79 (s, 3 H) 3,47 - 3,54 (m, 1 H) 3,33 (td, J = 8,46, 3,79 Hz, 1 H) 2,63 (t, J = 5,31 Hz, 3 H).

Ejemplo 22

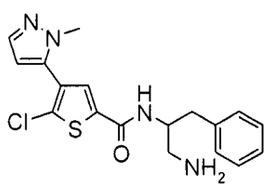


Preparación de *N*-[2-amino-1-(fenilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se sustituyó ácido 4,5-dibromo-2-furanocarboxílico por ácido 4-bromo-5-metil-2-tiofenocarboxílico (81 mg, 0,368 mmol) [de la Preparación 10]: LC-MS (ES) m/z 355

$(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,84 (d, J = 8,34 Hz, 1 H) 8,15 (s a, 3 H) 8,00 (s, 1 H) 7,52 (d, J = 1,77 Hz, 1 H) 7,24 - 7,31 (m, 4 H) 7,17 - 7,23 (m, 1 H) 6,36 (d, J = 1,77 Hz, 1 H) 4,35 (d, J = 3,03 Hz, 1 H) 3,78 (s, 3 H) 3,03 (dd, J = 6,82, 2,53 Hz, 1 H) 2,93 - 2,99 (m, 2 H) 2,90 (d, J = 6,06 Hz, 1 H) 2,38 (s, 3 H).

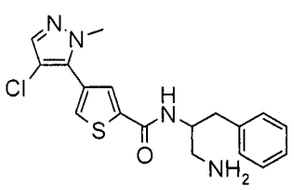
Ejemplo 23



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

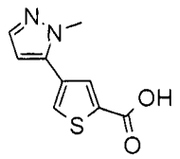
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se sustituyó ácido 4,5-dibromo-2-furanocarboxílico por ácido 4-bromo-5-cloro-2-tiofenocarboxílico (250 mg, 1,04 mmol) [de la Preparación 11]: LC-MS (ES) m/z 375 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 9,09 (d, J = 8,59 Hz, 1 H) 8,14 (s, 3 H) 8,10 (s a, 1 H) 7,55 (d, J = 1,77 Hz, 1 H) 7,25 - 7,32 (m, 4 H) 7,21 (dd, J = 6,19, 2,40 Hz, 1 H) 6,48 (d, J = 2,02 Hz, 1 H) 4,35 (d, J = 8,59 Hz, 1 H) 3,84 (s, 3 H) 2,99 (d, J = 10,86 Hz, 1 H) 2,89 - 2,96 (m, 3 H).

Ejemplo 24:



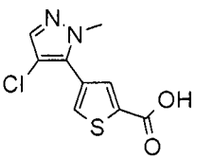
Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



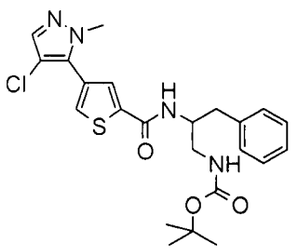
A una solución de ácido 4-bromo-2-tiofenocarboxílico (1 g, 4,83 mmol) en dioxano/H_2O (5:1, 16 ml) se le añadieron K_2CO_3 (2,7 g, 19 mmol), tetraquistrifenilfosfina Pd(0) (279 mg, 0,241 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 6,27 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 2 h y se añadieron más cantidad de tetraquistrifenilfosfina Pd(0) (279 mg, 0,241 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 6,27 mmol). Después de 12 h, la reacción se repartió entre NaOH 6 N y DCM. El valor del pH de la fase acuosa se ajustó a ~3 con HCl 3 M y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional (~1 g, cuant.): LCMS (ES) m/z = 209 $(M+H)^+$.

b) ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



Una solución de ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (600 mg, 2,88 mmol) y N-clorosuccinimida (384 mg, 2,88 mmol) en THF (14 ml) se agitó en un tubo cerrado herméticamente a 70°C. Después de 1 h, la solución se repartió entre H_2O y DCM, la fase acuosa se ajustó a pH 3 y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional (698 mg, cuant.): LCMS (ES) m/z = 243 $(M+H)^+$.

c) [2-({[4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



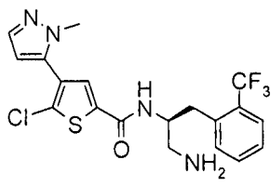
A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (350 mg, 1,45 mmol), (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (362 mg, 1,45 mmol) [de la Preparación 2] y diisopropiletil amina (1,3 ml, 7,23 mmol) en DCM (7 ml) se le añadió en una porción PyBrop (809 mg, 1,74 mmol). Después de 1 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z = 476 $(M+H)^+$.

d) N-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

Una solución de [2-({[4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (en bruto, de la parte c) en TFA-DCM (3 ml, 1:2) se agitó a 25ºC. Después de 30 min, la solución se concentró y el residuo se neutralizó a través de un lecho de sílice (MeOH al 4% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

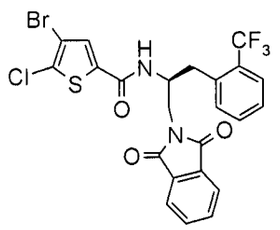
Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (90 mg, 17%-2 etapas) en forma de la sal HCl: LCMS (ES) m/z 476 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,75 (d, J = 8,08 Hz, 1 H) 8,10 (d, J = 1,52 Hz, 2 H) 8,08 (s, 3 H) 7,68 (s, 1 H) 7,26 - 7,32 (m, 4 H) 7,22 (dd, J = 6,06, 2,53 Hz, 1 H) 4,39 (s a, 1 H) 3,87 (s, 3 H) 2,91 (d, J = 7,33 Hz, 4 H).

Ejemplo 25:



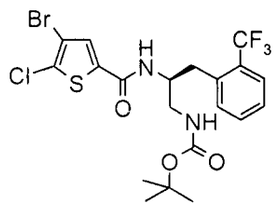
Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 4-bromo-5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



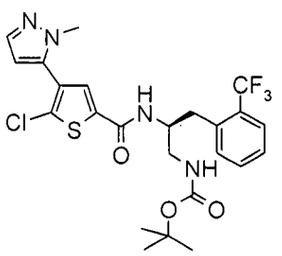
A una solución de ácido 4-bromo-5-cloro-2-tiofenocarboxílico (1,3 g, 5,42 mmol), PyBrOP (3 g, 6,5 mmol) y diisopropiletil amina (4,7 ml, 27,1 mmol) en DCM (54 ml) a 25°C se le añadió 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (2,0 g, 5,42 mmol) [preparado en la Preparación 6]. Después de 1 h, la solución se repartió entre H_2O y se lavó con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se usaron directamente: LCMS (ES) m/z = 572 $(M+H)^+$.

b) {(2S)-2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo



A una solución de 4-bromo-5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (en bruto, de la parte a) en THF-MeOH (1:1, 20 ml) se le añadió hidrazina (1,59 ml, 54,2 mmol). Después de 12 h, la solución se filtró y el filtrado se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 2% en DCM (NH_4OH al 1%)), produciendo la base libre que se disolvió en THF (25 ml) y se trató con Boc_2O (1,2 g, 5,31 mmol). Después de 30 min la solución se concentró, produciendo un polvo de color blanco del compuesto del título (800 mg, 27%-3 etapas): LCMS (ES) m/z = 542 $(M+H)^+$.

c) {(2S)-2-({[5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo



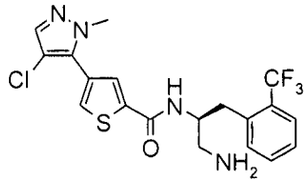
A una solución de {(2S)-2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo (750 mg, 1,38 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (762 mg, 5,52 mmol), tetraquistrifenilfosfina Pd(0) (80 mg, 69 μmol), y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (373 mg, 1,8 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 2 h, momento en el que se añadieron más cantidad de tetraquistrifenilfosfina Pd(0) (80 mg, 69 μmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (373 mg, 1,8 mmol). Después de 12 h, la solución se vertió en H_2O (100 ml) y se extrajo con DCM. Los extractos orgánicos se secaron (Na_2SO_4), se concentraron al vacío y se purificaron sobre gel de sílice (hexanos/EtOAc, 1:1) para dar el compuesto del título (194 mg, 26%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 544.

c) *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

Se disolvió {(2S)-2-({[5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo (194 mg, 0,357 mmol) en TFA-DCM (3 ml, 1:2) y la mezcla se agitó a 25°C. Después de 30 min, la solución se concentró con un azeótropo de tolueno y el residuo se neutralizó a través de un lecho de sílice (MeOH al 2-5% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

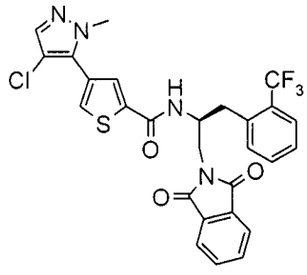
Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (134 mg, 85%) en forma de la sal HCl: LCMS (ES) m/z 444 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 9,10 (d, J = 9,09 Hz, 1 H) 8,11 (s, 1 H) 8,10 (s a, 3 H) 7,70 (d, J = 8,08 Hz, 1 H) 7,57 (d, J = 2,02 Hz, 2 H) 7,43 (s, 1 H) 6,49 (d, J = 2,02 Hz, 1 H) 4,47 (s a, 1 H) 3,85 (s, 3 H) 3,06 (d, J = 8,34 Hz, 4 H).

Ejemplo 26



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

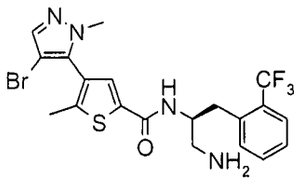
a) 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 24, con la excepción de que se sustituyó

d_6) ppm 8,65 (s a, 1 H) 8,01 (s a, 3 H) 7,80 (s, 1 H) 7,70 (s, 1 H) 7,25 - 7,32 (m, 4 H) 7,21 (td, J = 6,19, 2,78 Hz, 1 H) 4,31 - 4,35 (m, 1 H) 3,71 (s, 3 H) 2,86 - 2,92 (m, 4 H) 2,33 (s, 3 H).

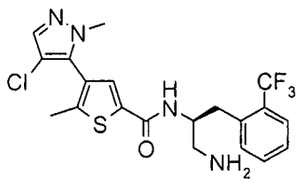
Ejemplo 28



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 26, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-bromo-5-metil-2-tiofenocarboxílico (1 g, 4,52 mmol) [de la Preparación 9] y se sustituyó NCS por NBS (325 mg, 2,43 mmol): LCMS (ES) m/z 502 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,81 (s a, 1 H) 8,05 (s a, 3 H) 7,83 - 7,90 (m, 1 H) 7,67 - 7,74 (m, 2 H) 7,53 - 7,60 (m, 2 H) 7,39 - 7,47 (m, 1 H) 4,48 (d, J = 5,05 Hz, 1 H) 3,68 - 3,76 (m, 3 H) 3,01 - 3,08 (m, 4 H) 2,33 (s, 3 H).

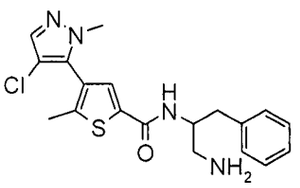
Ejemplo 29



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 26, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-bromo-5-metil-2-tiofenocarboxílico (1 g, 4,52 mmol) [de la Preparación 9]: LCMS (ES) m/z 457 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,76 (s a, 1 H) 8,03 (s a, 3 H) 7,86 (s, 1 H) 7,70 (s, 2 H) 7,53 - 7,60 (m, 2 H) 7,39 - 7,47 (m, 1 H) 4,46 (d, J = 9,35 Hz, 1 H) 3,72 (s, 3 H) 3,03 - 3,10 (m, 4 H) 2,34 (s, 3 H).

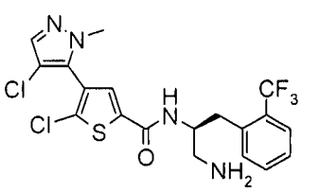
Ejemplo 30:



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

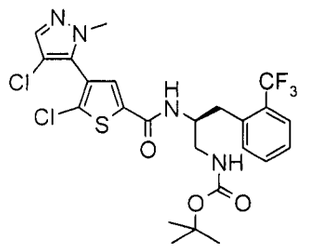
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 24, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-bromo-5-metil-2-tiofenocarboxílico (1 g, 4,52 mmol) [de la Preparación 9]: LCMS (ES) m/z 389 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,67 (s a, 1 H) 8,01 (s a, 3 H) 7,82 (s, 1 H) 7,70 (s, 1 H) 7,25 - 7,32 (m, 4 H) 7,19 - 7,23 (m, 1 H) 4,31 - 4,38 (m, 1 H) 3,71 (s, 3 H) 2,97 (s a, 2 H) 2,89 (t, J = 6,19 Hz, 2 H) 2,34 (s, 3 H).

Ejemplo 31:



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) {(2S)-2-({[5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo



Una solución de {(2S)-2-({[5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo (110 mg, 0,202 mmol) [preparado en el Ejemplo 25] y N-clorosuccinimida (35 mg, 0,263 mmol) en THF (2 ml) se agitó en un tubo cerrado herméticamente a 70°C. Después de 1 h, la solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional: LCMS (ES) m/z = 578 $(M+H)^+$.

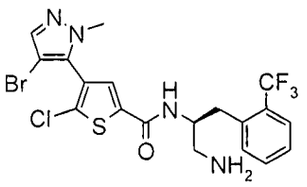
b) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

Se disolvió {(2S)-2-({[5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo (en bruto, de la parte a) en TFA-DCM (3 ml, 1:2) y la mezcla se agitó a 25°C. Después de 30 min, la solución se concentró y el residuo se neutralizó a través de un lecho de sílice (MeOH al 5% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (43 mg, 44%-2 etapas) en forma de la sal HCl: LCMS (ES) m/z 478 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 9,10 (d, J = 8,84 Hz, 1 H) 8,06 (s, 4 H) 7,75 (s, 1 H) 7,70 (d, J =

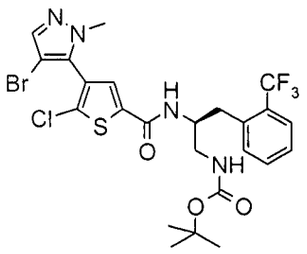
7,83 Hz, 1 H) 7,54 - 7,61 (m, 2 H) 7,43 (t, J = 7,45 Hz, 1 H) 4,47 (t, J = 8,84 Hz, 1 H) 3,78 (s, 3 H) 2,98 – 3,12 (m, 4 H).

Ejemplo 32:



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

a) {(2S)-2-({[4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo



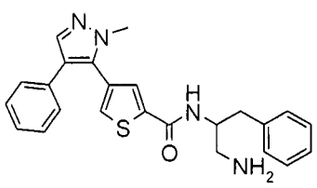
Una solución de {(2S)-2-({[5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo (121 mg, 0,22 mmol) [preparado en el Ejemplo 25] y N-bromosuccinimida (52 mg, 0,290 mmol) en THF (2 ml) se agitó en un tubo cerrado herméticamente a 70°C. Después de 1 h, la solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional: LCMS (ES) m/z = 622 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

Se disolvió {(2S)-2-({[4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tienil]carbonil}amino)-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo (en bruto, de la parte a) en TFA-DCM (3 ml, 1:2) y la mezcla se agitó a 25°C. Después de 30 min, la solución se concentró y el residuo se neutralizó a través de un lecho de sílice (MeOH al 5% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

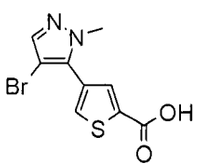
Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (42 mg, 44%-2 etapas) en forma de la sal HCl: LCMS (ES) m/z 522 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 9,13 (d, J = 9,09 Hz, 1 H) 8,17 (s a, 1 H) 8,05 (s, 3 H) 7,75 (s, 1 H) 7,69 (d, J = 7,83 Hz, 1 H) 7,54 - 7,61 (m, 2 H) 7,43 (t, J = 7,58 Hz, 1 H) 4,46 (d, J = 9,60 Hz, 1 H) 3,78 (s, 3 H) 2,99 – 3,13 (m, 4 H).

Ejemplo 33



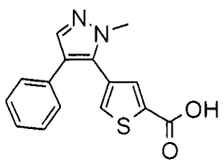
Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



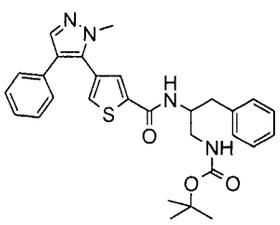
El compuesto del título se preparó en forma de un aceite de color naranja de acuerdo con el Ejemplo 24, con la excepción de que se sustituyó N-clorosuccinimida por N-bromosuccinimida (1 g, 5,77 mmol): LCMS (ES) m/z 288 $(M+H)^+$.

b) ácido 4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxílico



A una solución de ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (688 mg, 2,41 mmol) en dioxano/H_2O (5:1, 12 ml) se le añadieron K_2CO_3 (1,3 g, 9,6 mmol), tetraquistrifenilfosfina Pd(0) (139 mg, 0,120 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (293 mg, 2,41 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 2 h, momento en el que se añadieron más cantidad de tetraquistrifenilfosfina Pd(0) (139 mg, 0,120 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (293 mg, 2,41 mmol). Después de 12 h, la solución se vertió en H_2O y el valor del pH se ajustó a ~4 con HCl acuoso. La fase acuosa se extrajo varias veces con DCM y las fracciones orgánicas combinadas se secaron (Na_2SO_4) y se concentraron, produciendo el compuesto del título de color blanco que se usó directamente sin purificación adicional: LC-MS (ES) m/z = 284 $(M+H)^+$.

c) [2-({[4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



A una solución de ácido 4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxílico (341 mg, 1,2 mmol), (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (300 mg, 1,2 mmol) [de la Preparación 2] y diisopropiletil amina (1 ml, 6,01 mmol) en DCM (6 ml) se le añadió en una porción PyBrop (673 mg, 1,44 mmol). Después de 1 h, los contenidos de la reacción se repartieron entre

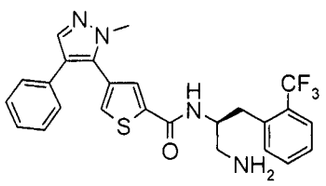
H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z = 517 $(M+H)^+$.

d) N-[2-amino-1-(fenilmetil)etil]-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida

Una solución de [2-({[4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (en bruto, de la parte c) en TFA-DCM (3 ml, 1:2) se agitó a 25ºC. Después de 30 min, la solución se concentró y el residuo se neutralizó a través de un lecho de sílice (MeOH al 4% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

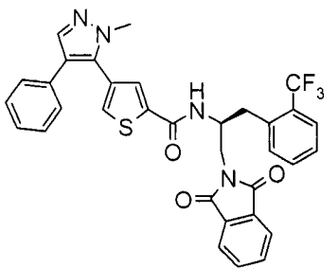
Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (105 mg, 21%-3 etapas) en forma de la sal HCl: LCMS (ES) m/z 417 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,82 (d, J = 8,34 Hz, 1 H) 8,14 (s a, 3 H) 7,96 (s, 1 H) 7,90 (d, J = 1,26 Hz, 1 H) 7,82 (s, 1 H) 7,29 (s, 1 H) 7,25 (t, J = 8,46 Hz, 9 H) 4,34 (dd, J = 7,45, 5,68 Hz, 1 H) 3,75 (s, 3 H) 2,94 - 3,00 (m, 2 H) 2,89 (dd, J = 6,82, 5,31 Hz, 2 H).

Ejemplo 34



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida



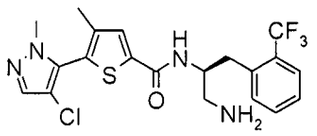
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 33, con la excepción de que se sustituyó (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo por 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (420 mg, 1,2 mmol) [de la Preparación 6]: LCMS (ES) m/z 615 $(M+H)^+$.

b) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida

A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida (en bruto, de la parte a) en THF-MeOH (1:1, 10 ml) se le añadió hidrazina (384 µl, 12 mmol). Después de 12 h, la solución se filtró y el filtrado se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 2% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

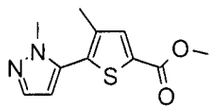
Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (40 mg, 7%) en forma de la sal HCl: LCMS (ES) m/z 485 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,78 (d, J = 9,09 Hz, 1 H) 8,05 (s a, 3 H) 7,91 (dd, J = 9,09, 1,26 Hz, 2 H) 7,83 (s, 1 H) 7,69 (d, J = 7,33 Hz, 1 H) 7,50 - 7,53 (m, 1 H) 7,43 (d, J = 7,58 Hz, 1 H) 7,47 (t, J = 6,82 Hz, 1 H) 7,23 - 7,30 (m, 4 H) 7,22 (s, 1 H) 4,47 (s a, 1 H) 3,75 (s, 3 H) 3,01 (d, J = 8,08 Hz, 4 H).

Ejemplo 35



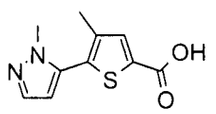
Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-cloro-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida

a) 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 5-bromo-4-metil-2-tiofenocarboxilato de metilo (1 g, 4,25 mmol) en dioxano/H_2O (5:1, 20 ml) se le añadieron K_2CO_3 (2,3 g, 17 mmol), bis(tri-t-butilfosfina)paladio (0) (108 mg, 0,213 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 5,52 mmol). La mezcla de reacción se calentó a 88ºC en un tubo cerrado herméticamente durante 2 h y se añadieron más cantidad de tetraquistrifenilfosfina Pd(0) (279 mg, 0,241 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 6,27 mmol). Después de 12 h, la reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional: LCMS (ES) m/z = 237 $(M+H)^+$.

b) ácido 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico

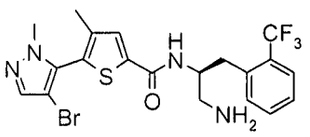


Una solución de 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (en bruto, de la parte a) en THF (4 ml) y NaOH 6 N (4 ml) se calentó a 70ºC. Después de 1 h, la solución se vertió en H_2O y el valor del pH se ajustó a ~4 con HCl acuoso. La fase acuosa se extrajo varias veces con DCM y las fracciones orgánicas combinadas se secaron (Na_2SO_4) y se concentraron, produciendo el compuesto del título en forma de un sólido de color blanco que se usó directamente sin purificación adicional: LCMS (ES) m/z = 223 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-cloro-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida

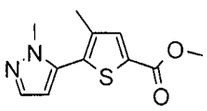
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 27, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (424 mg, 1,92 mmol): LCMS (ES) m/z 457 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,84 (d, J = 8,84 Hz, 1 H) 8,05 (s a, 3 H) 7,84 (s, 1 H) 7,74 (s, 1 H) 7,71 (d, J = 8,08 Hz, 1 H) 7,56 - 7,63 (m, 2 H) 7,44 (t, J = 7,20 Hz, 1 H) 4,47 - 4,54 (m, 1 H) 3,70 (s, 3 H) 2,93 - 3,12 (m, 4 H) 2,10 (s, 3 H).

Ejemplo 36



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-bromo-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida

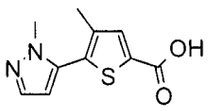
a) 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 5-bromo-4-metil-2-tiofenocarboxilato de metilo (1 g, 4,25 mmol) en dioxano/H_2O (5:1, 20 ml) se le añadieron K_2CO_3 (2,3 g, 17 mmol), bis(tri-t-butilfosfina)paladio (0) (108 mg, 0,213 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 5,52 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 2 h y se añadieron más cantidad de tetraquistrifenilfosfina Pd(0) (279 mg, 0,24 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 6,27 mmol). Después de 12 h, la reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se

concentraron y se usaron directamente sin purificación adicional: LCMS (ES) m/z = 237 $(M+H)^+$.

b) ácido 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico

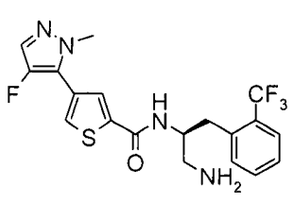


Una solución de 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (en bruto, de la parte a) en THF (4 ml) y NaOH 6 N (4 ml) se calentó a 70°C. Después de 1 h, la solución se vertió en H_2O y el valor del pH se ajustó a ~4 con HCl acuoso. La fase acuosa se extrajo varias veces con DCM y las fracciones orgánicas combinadas se secaron (Na_2SO_4) y se concentraron, produciendo el compuesto del título de color blanco que se usó directamente sin purificación adicional: LCMS (ES) m/z = 223 $(M+H)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-bromo-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida

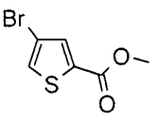
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 26, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (424 mg, 1,92 mmol) y se sustituyó N-clorosuccinimida por N-bromosuccinimida (376 mg, 2,11 mmol): LCMS (ES) m/z 502 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,84 (d, J = 9,09 Hz, 1 H) 8,05 (s a, 3 H) 7,83 (s, 1 H) 7,67 - 7,74 (m, 2 H) 7,60 (c, J = 7,83 Hz, 2 H) 7,40 - 7,47 (m, 1 H) 4,50 (d, J = 4,04 Hz, 1 H) 3,71 (s, 3 H) 2,98-3,12 (m, 4 H) 2,09 (s, 3 H).

Ejemplo 37:



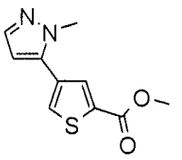
Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 4-bromo-2-tiofenocarboxilato de metilo



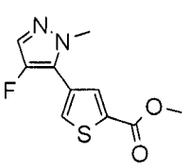
A una solución de ácido 4-bromo-2-tiofenocarboxílico (4 g, 19 mmol) en MeOH (100 ml) se le añadió gota a gota H_2SO_4 (5 ml) a 25°C. La solución se agitó durante 12 h a 50°C, se vertió en hielo-H_2O y el valor del pH se ajustó a ~11 con NaOH acuoso. La fase acuosa se extrajo varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente (4,27 g, cuant.): LCMS (ES) m/z 222 $(M+H)^+$.

b) 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



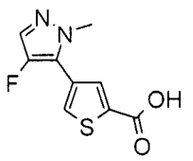
A una solución de 4-bromo-2-tiofenocarboxilato de metilo (1 g, 4,52 mmol) en dioxano/H_2O (5:1, 16 ml) se le añadieron K_2CO_3 (2,7 g, 19 mmol), bis(tri-t-butilfosfina)paladio (0) (116 mg, 0,226 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,2 g, 5,88 mmol). La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente. Después de 1 h, la reacción se repartió entre H_2O y DCM y la fase acuosa se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z 223 $(M+H)^+$.

c) 4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



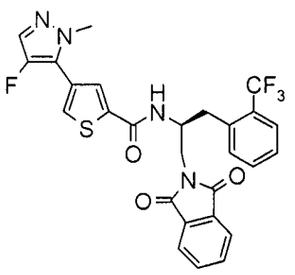
Una solución de 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (330 mg, 1,49 mmol) y selectfluor® (793 mg, 2,23 mmol) en THF (7 ml) y H_2O (500 µl) se agitó en un tubo cerrado herméticamente a 70°C. Después de 1 h, se añadió más cantidad de selectfluor (793 mg, 2,23 mmol) y la solución se agitó durante 12 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo el compuesto del título (126 mg, 33%) en forma de un sólido de color blanco: LCMS (ES) m/z = 241 $(M+H)^+$.

d) ácido 4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



Una solución de 4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (126 mg, 0,53 mmol) en THF (1 ml) y NaOH 6 N (1 ml) se calentó a 70°C. Después de 1 h, la solución se vertió en H_2O y el valor del pH se ajustó a ~4 con HCl acuoso. La fase acuosa se extrajo varias veces con DCM y las fracciones orgánicas combinadas se secaron (Na_2SO_4) y se concentraron, produciendo el compuesto del título de color blanco que se usó directamente sin purificación adicional: LCMS (ES) m/z = 227 $(M+H)^+$.

e) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

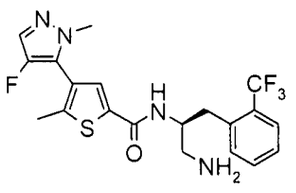


A una solución de ácido 4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (84 mg, 0,372 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (130 mg, 0,372 mmol) [de la Preparación 6] y diisopropiletil amina (323 µl, 1,86 mmol) en DCM (4 ml) se le añadió en una porción PyBrop (208 mg, 0,446 mmol). Después de 1 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, MeOH al 0,5%-DCM), produciendo el compuesto del título (135 mg, 65%) en forma de un sólido de color blanco: LCMS (ES) m/z = 557 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (135 mg, 0,242 mmol) en THF-MeOH (1:1, 2 ml) se le añadió hidrazina (75 µl, 2,42 mmol). Después de 12 h, la solución se filtró y el filtrado se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 3% en DCM (NH_4OH al 1%)). El compuesto del título se purificó adicionalmente por cromatografía de fase inversa Gilson usando un gradiente de fase móvil al 5-95%, produciendo la sal TFA del compuesto del título que se neutralizó a través de un lecho de sílice ((MeOH al 5% en DCM (NH_4OH al 1%)) y después se transfirió a la sal HCl usando exceso de HCl 4 M en dioxano (40 mg, 26%): LCMS (ES) m/z 427 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) δ ppm 8,88 (d, J = 8,84 Hz, 1 H) 8,13 (s, 1 H) 8,06 (s a, 3 H) 7,70 (d, J = 7,83 Hz, 1 H) 7,55 - 7,62 (m, 3 H) 7,54 (s a, 1 H) 7,41 (d, J = 2,53 Hz, 1 H) 4,49 (d, J = 5,05 Hz, 1 H) 3,92 (s, 3 H) 2,99 - 3,11 (m, 4 H).

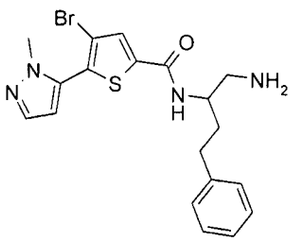
Ejemplo 38



Preparación de *N*-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 37, con la excepción de que se sustituyó 4-bromo-2-tiofenocarboxilato de metilo por 4-bromo-5-metil-2-tiofenocarboxilato de metilo (1 g, 4,26 mmol) [de la Preparación 11]: LCMS (ES) m/z 441 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d6) ppm 8,78 (d, J = 9,60 Hz, 1 H) 8,03 (s a, 3 H) 7,91 (s, 1 H) 7,69 (d, J = 7,83 Hz, 1 H) 7,62 (d, J = 4,55 Hz, 1 H) 7,52 - 7,59 (m, 2 H) 7,39 - 7,46 (m, 1 H) 4,47 (s a, 1 H) 3,74 (s, 3 H) 3,06 (s a, 4 H) 2,36 (s, 3 H).

Ejemplo 39:

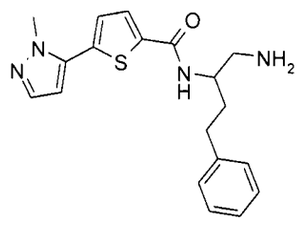


Preparación de *N*-[1-(aminometil)-3-fenilpropil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo (0,44 g, 1,7 mmol) [de la Preparación 4]: LC-MS (ES) m/z = 435 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) ppm 1,92 - 2,22 (m, 2 H) 2,71 - 2,82 (m, 2 H) 3,02 - 3,11 (m, 1 H) 3,12 - 3,24 (m, 1 H) 3,88 (s, 3 H) 4,30 (s, 1

H) 6,59 (d, *J* = 1,77 Hz, 1 H) 7,17 (t, *J* = 7,07 Hz, 1 H) 7,22 - 7,29 (m, 4 H) 7,67 (d, *J* = 1,77 Hz, 1 H) 7,85 (s, 1 H).

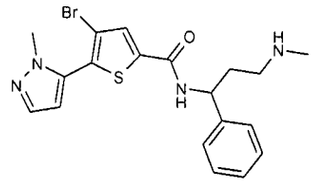
Ejemplo 40



Preparación de *N*-[1-(aminometil)-3-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó ácido 4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico por ácido 5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (223 mg, 1,07 mmol) y se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo (0,51 g, 1,9 mmol) [de la Preparación 4]: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 1,87 - 1,99 (m, 2 H) 2,69 - 2,91 (m, 4 H) 4,00 - 4,07 (m, 3 H) 4,08 - 4,16 (m, 1 H) 6,56 (d, *J* = 2,02 Hz, 1 H) 7,15 (t, *J* = 6,95 Hz, 1 H) 7,20 - 7,28 (m, 4 H) 7,35 (d, *J* = 3,79 Hz, 1 H) 7,51 (d, *J* = 1,77 Hz, 1 H) 7,79 (d, *J* = 3,79 Hz, 1 H).

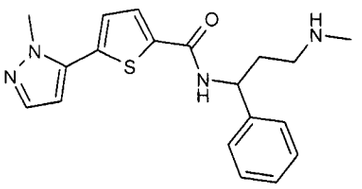
Ejemplo 41



Preparación de 4-bromo-*N*-[3-(metilamino)-1-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (3-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo (289 mg, 1,09 mmol) [de la Preparación 12]: LC-MS (ES) m/z 435 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,12 - 2,23 (m, 2 H) 2,45 - 2,52 (m, 3 H) 2,64 - 2,74 (m, 1 H) 2,76 (dd, *J* = 8,72, 5,94 Hz, 1 H) 3,77 - 3,88 (m, 3 H) 5,10 - 5,20 (m, 1 H) 6,52 (d, *J* = 2,02 Hz, 1 H) 7,30 (d, *J* = 6,82 Hz, 1 H) 7,35 - 7,45 (m, 4 H) 7,57 (d, *J* = 1,77 Hz, 1 H) 7,89 (s, 1 H).

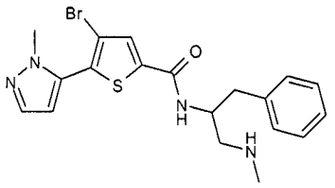
Ejemplo 42



Preparación de *N*-[3-(metilamino)-1-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (2-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (3-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo (430 mg, 1,63 mmol) [de la Preparación 12] y se sustituyó ácido 4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico por ácido 5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (224 mg, 1,08 mmol): LC-MS (ES) m/z 355 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,18 - 2,28 (m, 2 H) 2,55 (s, 3 H) 2,77 - 2,85 (m, 1 H) 2,87 (dd, *J* = 8,84, 5,81 Hz, 1 H) 4,01 (s, 3 H) 5,19 (dd, *J* = 8,59, 6,57 Hz, 1 H) 6,55 (d, *J* = 2,02 Hz, 1 H) 7,31 (d, *J* = 7,07 Hz, 1 H) 7,34 - 7,41 (m, 3 H) 7,44 - 7,47 (m, 2 H) 7,50 (d, *J* = 2,02 Hz, 1 H) 7,85 (d, *J* = 4,04 Hz, 1 H).

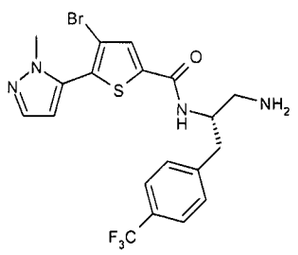
Ejemplo 43



Preparación de 4-bromo-*N*-[2-(metilamino)-1-(fenilmetil)etil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (2-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo (0,26 g, 1,09 mmol) [de la Preparación 12]: LC-MS (ES) m/z 435 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,60 (s, 3 H) 2,90 - 3,01 (m, 2 H) 3,06 (d, *J* = 6,57 Hz, 2 H) 3,83 (s, 3 H) 4,48 - 4,58 (m, 1 H) 6,52 (d, *J* = 1,77 Hz, 1 H) 7,17 - 7,27 (m, 1 H) 7,27 - 7,33 (m, 4 H) 7,57 (d, *J* = 2,02 Hz, 1 H) 7,77 (s, 1 H).

Ejemplo 44

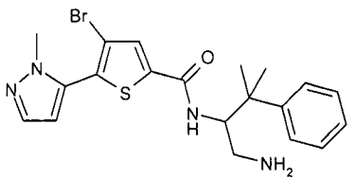


Preparación de *N*-((1*S*)-2-amino-1-{[4-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 6, con la excepción de que se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-{(2*S*)-2-amino-3-[4-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (0,22 g, 0,62 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna para producir el compuesto del título, que se purificó adicionalmente por

cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 489 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,04 - 3,30 (m, 4 H) 3,81 - 3,85 (m, 3 H) 4,59 (dd, *J* = 6,32, 3,28 Hz, 1 H) 6,52 (d, *J* = 2,02 Hz, 1 H) 7,50 (d, *J* = 8,08 Hz, 2 H) 7,58 (d, *J* = 2,02 Hz, 1 H) 7,64 (d, *J* = 8,08 Hz, 2 H) 7,73 (s, 1 H).

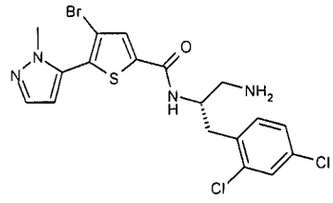
Ejemplo 45



Preparación de *N*-[1-(aminometil)-2-metil-2-fenilpropil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (194 mg, 0,68 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-(2-amino-3-metil-3-fenilbutil)-1*H*-isoindolo-1,3(2*H*)-diona (0,20 g, 0,58 mmol) [preparada de acuerdo con la preparación 16]. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 448 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 1,40 (s, 3 H) 1,47 (s, 3 H) 2,85 - 2,92 (m, 1 H) 3,01 (d, *J* = 11,37 Hz, 1 H) 3,83 - 3,86 (m, 3 H) 4,74 (dd, *J* = 11,37, 2,27 Hz, 1 H) 6,54 (d, *J* = 2,02 Hz, 1 H) 7,28 (t, *J* = 7,33 Hz, 1 H) 7,41 (t, *J* = 7,71 Hz, 3 H) 7,52 (d, *J* = 7,58 Hz, 2 H) 7,59 (d, *J* = 2,02 Hz, 1 H) 7,89 (s, 1 H).

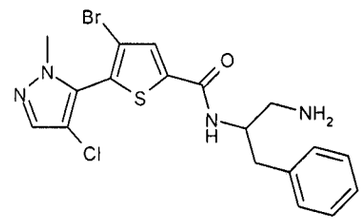
Ejemplo 46



Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (135 mg, 0,47 mmol) y se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 2-[(2*S*)-2-amino-3-(2,4-diclorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (153 mg, 0,44 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 491 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,03 (dd, *J* = 13,89, 9,35 Hz, 1 H) 3,14 - 3,21 (m, 1 H) 3,21 - 3,29 (m, 2 H) 3,84 (s, 3 H) 4,62 - 4,70 (m, 1 H) 6,53 (d, *J* = 2,02 Hz, 1 H) 7,28 - 7,32 (m, 1 H) 7,33 - 7,37 (m, 1 H) 7,51 (d, *J* = 2,02 Hz, 1 H) 7,58 (d, *J* = 2,02 Hz, 1 H) 7,73 - 7,76 (m, 1 H).

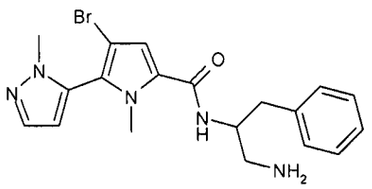
Ejemplo 47



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

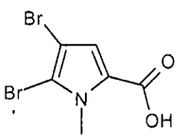
El compuesto del título se preparó en forma de un sólido de color amarillo pálido de acuerdo con el procedimiento del Ejemplo 30, con la excepción de que se sustituyó ácido 4-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (2,84 g, 9,9 mmol): LC-MS (ES) m/z 457 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,95 - 3,07 (m, 4 H) 3,75 (s, 3 H) 4,44 (dd, *J* = 6,44, 4,93 Hz, 1 H) 7,18 - 7,24 (m, 1 H) 7,27 - 7,32 (m, 4 H) 7,59 (s, 1 H) 7,86 (s, 1 H).

Ejemplo 48



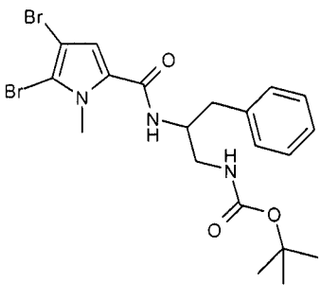
Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-bromo-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida

a) ácido 4,5-dibromo-1-metil-1*H*-pirrol-2-carboxílico



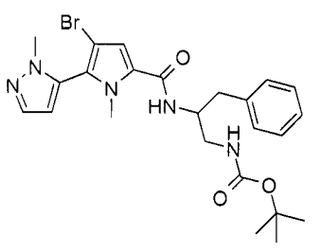
Se añadió en porciones NBS (6,3 g, 35,4 mmol) durante 15 minutos a una solución agitada de ácido 1-metil-1*H*-pirrol-2-carboxílico (2,1 g, 16,78 mmol) en DMF (30 ml) a 0°C. Después de que se completara la adición, la mezcla se llevó lentamente a 70°C. Después de 1 h, la solución se repartió entre H_2O-$CHCl_3$, la fase acuosa se ajustó a pH 3 y la fase acuosa se lavó varias veces con $CHCl_3$. Las fracciones orgánicas combinadas se secaron (Na_2SO_4) y se concentraron al vacío para producir una mezcla 3:4 de ácido 5-bromo-1-metil-1*H*-pirrol-2-carboxílico y ácido 4,5-dibromo-1-metil-1*H*-pirrol-2-carboxílico (3,4 g) que se usó directamente sin purificación adicional: LCMS (ES) m/z = 206/286 $(M+H)^+$.

b) (2-{[(4,5-dibromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo



A una solución de ácido 5-bromo-1-metil-1*H*-pirrol-2-carboxílico y ácido 4,5-dibromo-1-metil-1*H*-pirrol-2-carboxílico (1,3 g), (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (1,2 g, 4,8 mmol) [de la Preparación 2] y PyBrop (2,6 g, 5,6 mmol) en $CHCl_3$ (30 ml) se le añadió diisopropiletil amina (2,8 ml, 16,1 mmol). La mezcla de reacción se agitó durante una noche, se absorbió sobre sílice y se purificó por cromatografía en columna [1:3 de EtOAc/hexanos] para dar una mezcla 1:1 de (2-{[(5-bromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo y (2-{[(4,5-dibromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (800 mg): LCMS (ES) m/z = 438/518 $(M+H)^+$.

c) [2-({[4-bromo-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-il]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



A una solución de una mezcla 1:1 de (2-{[(5-bromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)cabamato de 1,1-dimetiletilo y (2-{[(4,5-dibromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (307 mg) en dioxano/H_2O (5:1, 5,6 ml) se le añadieron Cs_2CO_3 (800 mg, 2,5 mmol), tetraquistrifenilfosfina Pd(0) (44 mg, 0,04 mmol) y 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (157 mg, 0,75 mmol). La mezcla de reacción se

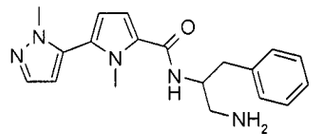
calentó a 88ºC en un tubo cerrado herméticamente durante 2 h, tiempo después del cual se añadieron más cantidad de tetraquistrifenilfosfina Pd(0) (20 mg, 0,02 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (177 mg, 0,85 mmol). Después de 12 h, la mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna para dar dos isómeros: el compuesto del título [2-({[4-bromo-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-il]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (17 mg, 0,033 mmol) y [2-({[1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-il]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (20 mg, 0,05 mmol).

d) *N*-[2-amino-1-(fenilmetil)etil]-4-bromo-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida

Se trataron [3-{[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tienil]amino}-3-oxo-2-(fenilmetil)propil]carbamato de 1,1-dimetiletilo (0,045 g, 0,09 mmol) disuelto en $CHCl_3$ (4 ml) y MeOH (1 ml) con HCl 4 M en dioxano (2 ml). Después de agitar durante 18 h a TA, la solución de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título en forma de un sólido de color blanco.

El compuesto neutro de la etapa anterior se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O (150 l) y se concentró, produciendo la sal HCl del compuesto del título: LC-MS (ES) m/z 418 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,76 - 2,98 (m, 4 H) 3,57 (d, *J* = 2,78 Hz, 3 H) 3,71 (d, *J* = 1,26 Hz, 3 H) 4,28 (ddd, *J* = 8,27, 5,12, 2,78 Hz, 1 H) 6,44 (dd, *J* = 7,58, 2,02 Hz, 1 H) 6,85 (s, 1 H) 7,18 - 7,24 (m, 1 H) 7,27 - 7,32 (m, 4 H) 7,61 (d, *J* = 2,02 Hz, 1 H).

Ejemplo 49

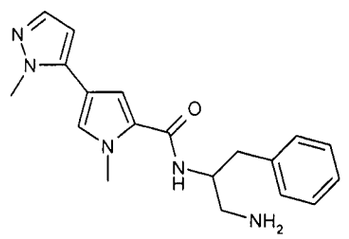


Preparación de *N*-[2-amino-1-(fenilmetil)etil]-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida

Se trató [2-({[1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-il]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (20 mg, 0,05 mmol) [preparado en el Ejemplo 48] en $CHCl_3$ (4 ml) y MeOH (1 ml) con HCl 4 M en dioxano (2 ml). Después de agitar durante 18 h a TA, la solución de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título.

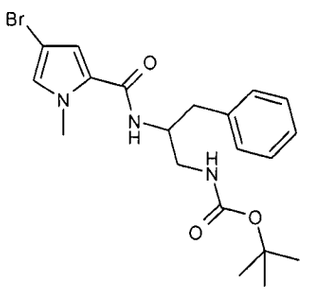
El compuesto anterior se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O (150 l) y se concentró, produciendo la sal HCl del compuesto del título: LC-MS (ES) m/z 338 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,74 - 2,81 (m, 1 H) 2,83 - 2,90 (m, 2 H) 2,92 - 2,98 (m, 1 H) 3,63 (s, 3 H) 3,76 (s, 3 H) 4,29 (ddd, *J* = 8,02, 5,12, 2,53 Hz, 1 H) 6,27 (d, *J* = 4,04 Hz, 1 H) 6,39 (d, *J* = 2,02 Hz, 1 H) 6,80 (d, *J* = 4,04 Hz, 1 H) 7,20 (td, *J* = 5,87, 2,65 Hz, 1 H) 7,26 - 7,31 (m, 4 H) 7,57 (d, *J* = 2,02 Hz, 1 H).

Ejemplo 50



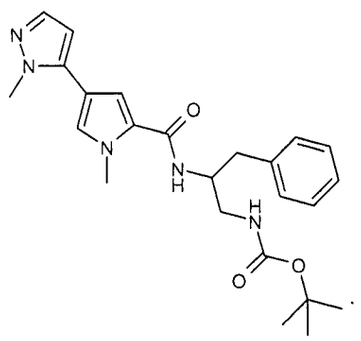
Preparación de *N*-[2-amino-1-(fenilmetil)etil]-1-metil-4-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida

a) (2-{[(4-bromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-bromo-1-metil-1*H*-pirrol-2-carboxílico (610 mg, 3,0 mmol), (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (748 mg, 2,99 mmol) [preparado de acuerdo con el procedimiento de la Preparación 2] y PyBrop (1,71 g, 3,67 mmol) en cloroformo (15 ml). Se añadió DIEA (1,8 ml, 10,3 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (Hex/EtOAc), produciendo el compuesto del título (335 mg, 26%): LC-MS (ES) m/z = 438 $(M+H)^+$.

b) [2-({[1-metil-4-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-il]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



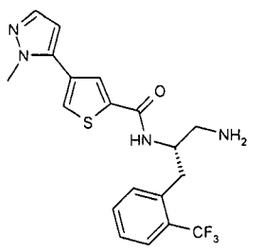
A una solución de (2-{[(4-bromo-1-metil-1*H*-pirrol-2-il)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (313 mg, 0,717 mmol) en dioxano/H_2O (4:1, 6,25 ml) se le añadieron Cs_2CO_3 (840 mg, 2,6 mmol), tetraquistrifenilfosfina Pd(0) (62 mg, 0,05 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (202 mg, 1,04 mmol). La mezcla de reacción se calentó a 80ºC en un tubo cerrado herméticamente durante 12 h y después se repartió entre H_2O y $CHCl_3$. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío, se absorbieron sobre gel de sílice y se purificaron por cromatografía en columna (EtOAc al 35%/Hex), produciendo el compuesto del título (285 mg, 91%): LC-MS (ES) m/z = 438 $(M+H)^+$.

c) *N*-[2-amino-1-(fenilmetil)etil]-1-metil-4-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida

Se añadió HCl en dioxano (4 M, 2 ml) a una solución de [2-({[1-metil-4-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-il]carbonil}amino)-3-fenilpropil]carbamato de 1,1-

dimetiletilo (285 mg, 0,65 mmol) en CHCl3/MeOH (10:1, 10 ml), produciendo el compuesto del título en forma de un sólido de color blanco (71 mg, 0,21 mmol, 32%): LC-MS (ES) m/z 338 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) ppm 2,77 - 2,93 (m, 4 H) 3,86 (s, 3 H) 3,92 (s, 3 H) 4,29 (ddd, *J* = 8,15, 4,74, 2,02 Hz, 1 H) 6,30 (d, *J* = 2,02 Hz, 1 H) 6,94 (d, *J* = 1,77 Hz, 1 H) 7,14 (d, *J* = 1,77 Hz, 1 H) 7,19 (td, *J* = 5,56, 3,03 Hz, 1 H) 7,25 - 7,30 (m, 4 H) 7,41 (d, *J* = 1,77 Hz, 1 H).

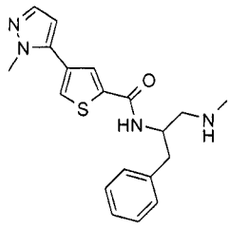
Ejemplo 51



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (232 mg, 1,11 mmol). La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 409 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) ppm 3,09 - 3,30 (m, 4 H) 3,97 - 4,00 (m, 3 H) 4,62 - 4,72 (m, 1 H) 6,48 (d, *J* = 2,02 Hz, 1 H) 7,43 (ddd, *J* = 8,08, 4,42, 4,17 Hz, 1 H) 7,51 - 7,56 (m, 3 H) 7,72 (d, *J* = 7,83 Hz, 1 H) 7,89 - 7,93 (m, 2 H).

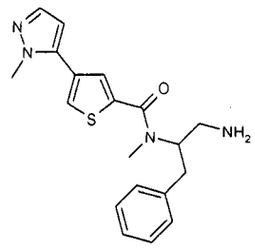
Ejemplo 52



Preparación de *N*-[2-(metilamino)-1-(fenilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (2-amino-3-fenilpropil)metilcarbamato de 1,1-dimetiletilo (0,32 g, 1,2 mmol) [de la Preparación 13] y se sustituyó ácido 4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (220 mg, 1,06 mmol): LC-MS (ES) m/z 355 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,41 (s, 3 H) 2,81 (td, *J* = 11,81, 7,96 Hz, 2 H) 2,87 - 2,97 (m, 2 H) 3,96 (s, 3 H) 4,43 - 4,52 (m, 1 H) 6,45 (d, *J* = 1,52 Hz, 1 H) 7,16 - 7,23 (m, 1 H) 7,25 - 7,30 (m, 4 H) 7,50 (d, *J* = 1,52 Hz, 1 H) 7,85 (d, *J* = 13,14 Hz, 2 H).

Ejemplo 53

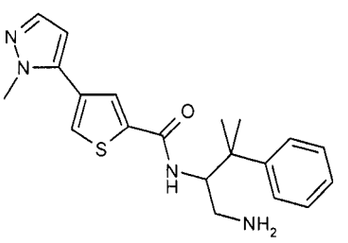


Preparación de *N*-[2-amino-1-(fenilmetil)etil]-*N*-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-[2-(metilamino)-3-fenilpropil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,7 mmol)

[preparada de acuerdo con el procedimiento de la Preparación 6] y se sustituyó ácido 4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (150 mg, 0,72 mmol). La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 355 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,86 (s, 3 H) 2,97 (dd, *J* = 14,02, 8,72 Hz, 2 H) 3,12 - 3,23 (m, 2 H) 3,70 (m, 1 H) 3,97 (s, 3 H) 6,47 (d, *J* = 2,02 Hz, 1 H) 7,30 - 7,35 (m, 1 H) 7,37 - 7,43 (m, 5 H) 7,51 (d, *J* = 2,02 Hz, 1 H) 7,88 (d, *J* = 1,52 Hz, 1 H) 7,94 (d, *J* = 1,52 Hz, 1 H).

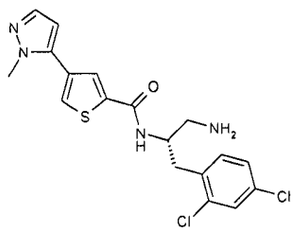
Ejemplo 54



Preparación de *N*-[1-(aminometil)-2-metil-2-fenilpropil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (129 mg, 0,62 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-(2-amino-3-metil-3-fenilbutil)-1*H*-isoindolo-1,3(2*H*)-diona (0,20 g, 0,58 mmol) [preparada de acuerdo con el procedimiento de la Preparación 14]: LC-MS (ES) m/z 369 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 1,36 (s, 3 H) 1,41 (s, 3 H) 2,61 (d, *J* = 6,82 Hz, 2 H) 3,99 (s, 3 H) 4,49 (t, *J* = 6,95 Hz, 1 H) 6,49 (d, *J* = 1,77 Hz, 1 H) 7,23 (t, *J* = 7,33 Hz, 1 H) 7,36 (t, *J* = 7,71 Hz, 2 H) 7,47 - 7,52 (m, 3 H) 7,89 (d, *J* = 1,26 Hz, 1 H) 8,00 (d, *J* = 1,52 Hz, 1 H)).

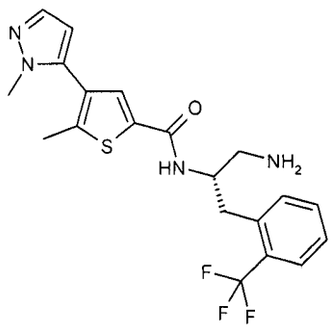
Ejemplo 55



Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

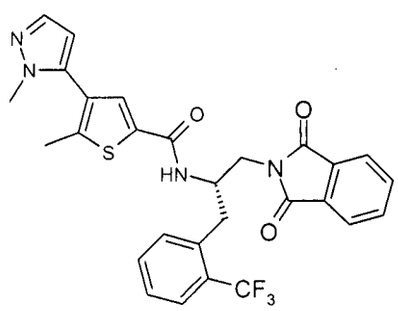
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (99 mg, 0,48 mmol) y se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 2-[(2*S*)-2-amino-3-(2,4-diclorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (155 mg, 0,44 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 411 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,05 - 3,28 (m, 4 H) 3,97 (s, 3 H) 4,63 - 4,72 (m, 1 H) 6,47 (d, *J* = 2,02 Hz, 1 H) 7,26 - 7,29 (m, 1 H) 7,34 - 7,37 (m, 1 H) 7,49 (d, *J* = 2,27 Hz, 1 H) 7,51 (d, *J* = 2,02 Hz, 1 H) 7,86 (d, *J* = 1,52 Hz, 1 H) 7,90 (d, *J* = 1,52 Hz, 1 H).

Ejemplo 56



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



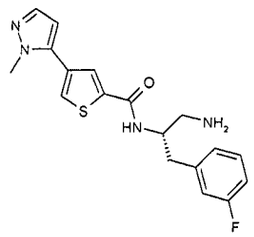
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (206 mg, 0,93 mmol) [preparado de acuerdo con el procedimiento de la Preparación 9], 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (209 mg, 0,60 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y PyBrop (340 mg, 0,73 mmol) en cloroformo (15 ml). Se añadió DIEA (0,81 ml, 4,65 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. Después de que se completara, la mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 75%/Hex), produciendo el compuesto del título (112 mg, 0,203 mmol, 22%): LC-MS (ES) m/z = 553 $(M+H)^+$

b) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadieron *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (112 mg, 0,203 mmol) en tetrahidrofurano (THF) (6 ml) y metanol (1 ml). Se añadió hidrazina (40 µl, 1,3 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. Después de que se completara, la mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (43 mg, 0,102 mmol, rendimiento de 50%): LC-MS (ES) m/z 423 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,38 (s, 3 H) 3,01 (m, 1 H) 3,08 (d, *J* = 6,57 Hz, 3 H) 3,76 - 3,83 (m, 3 H) 4,47 (m, 1 H) 6,37 (d, *J* = 2,02 Hz, 1 H) 7,41 (t, *J* = 7,58 Hz, 1 H) 7,50 - 7,57 (m, 2 H) 7,57 - 7,63 (m, 1 H) 7,68 (d, *J* = 7,58 Hz, 1 H) 8,04 (d, *J* = 9,09 Hz, 1 H) 8,15 (s, 3 H) 8,96 (s, 1 H).

Ejemplo 57

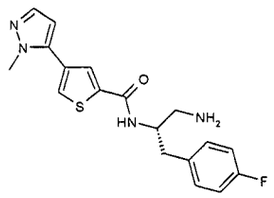


Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (222 mg, 1,07 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (357 mg, 1,2 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,96 - 3,06 (m, 4 H) 3,92 - 3,98 (m, 3 H) 4,40 (dd, *J*

= 8,08, 5,56 Hz, 1 H) 6,48 (d, *J* = 1,77 Hz, 1 H) 7,02 (td, *J* = 8,46, 2,02 Hz, 1 H) 7,14 (t, *J* = 8,08 Hz, 2 H) 7,26 - 7,35 (m, 1 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,99 (d, *J* = 1,26 Hz, 1 H) 8,16 - 8,27 (m, 3 H) 8,34 (d, *J* = 1,26 Hz, 1 H) 9,08 (d, *J* = 8,34 Hz, 1 H).

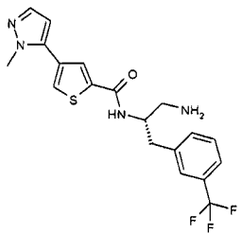
Ejemplo 58



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (138 mg, 0,66 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-[(2*S*)-2-amino-3-(4-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (196 mg, 0,66 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,80 - 3,03 (m, 4 H) 3,89 - 3,97 (m, 3 H) 4,30 - 4,40 (m, 1 H) 6,45 (d, *J* = 1,77 Hz, 1 H) 7,12 (t, *J* = 8,84 Hz, 2 H) 7,29 (dd, *J* = 8,34, 5,56 Hz, 2 H) 7,48 (d, *J* = 1,77 Hz, 1 H) 7,92 (s a, 3 H) 7,96 (d, *J* = 1,26 Hz, 1 H) 8,02 (d, *J* = 1,26 Hz, 1 H) 8,58 (d, *J* = 8,84 Hz, 1 H).

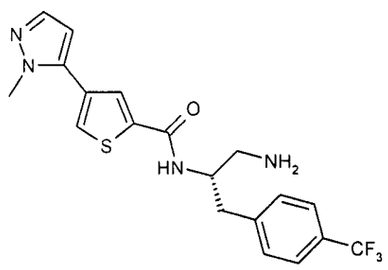
Ejemplo 59



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (189 mg, 0,91 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (297 mg, 0,85 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 3,06 (d, *J* = 7,07 Hz, 4 H) 3,91 - 3,98 (m, 3 H) 4,35 - 4,45 (m, 1 H) 6,46 (d, *J* = 1,77 Hz, 1 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,49 - 7,57 (m, 2 H) 7,58 - 7,63 (m, 1 H) 7,69 (s, 1 H) 7,98 (d, *J* = 1,52 Hz, 1 H) 8,23 (s, 3 H) 8,32 (d, *J* = 1,26 Hz, 1 H) 9,11 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 60

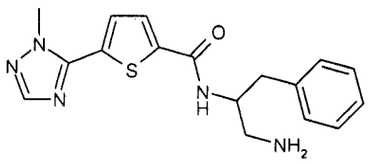


Preparación de *N*-((1*S*)-2-amino-1-{[4-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó

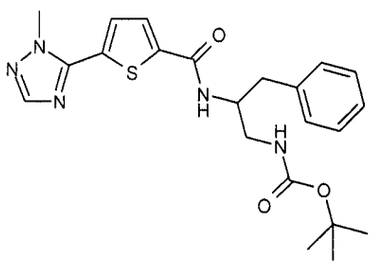
ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (240 mg, 0,9 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-{(2*S*)-2-amino-3-[4-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (278 mg, 0,80 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 3,04 (m, 4 H) 3,96 (s, 3 H) 4,42 (s, 1 H) 6,44 - 6,49 (m, 1 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,52 (d, *J* = 7,83 Hz, 2 H) 7,66 (d, *J* = 8,08 Hz, 2 H) 8,01 (s, 1 H) 8,05 – 8,32 (m a, 3H) 8,34 (m, 1H) 8,9 – 9,2 (s a, 1 H).

Ejemplo 61



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tiofenocarboxamida

a) [2-({[5-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



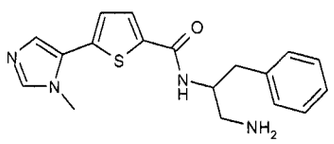
A una solución de [3-fenil-2-({[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-tienil]carbonil}amino)propil]carbamato de 1,1-dimetiletilo (154 mg, 0,32 mmol) [preparada de acuerdo con el procedimiento del Ejemplo 3] en dioxano/H_2O (5:1, 3,1 ml) se le añadieron Cs_2CO_3 (415 mg, 1,27 mmol), tetraquistrifenilfosfina Pd(0) (29 mg, 0,03 mmol) y 5-yodo-1-metil-1*H*-1,2,4-triazol (95 mg, 0,46 mmol) [preparado de acuerdo con el procedimiento de la Preparación 15]. La mezcla de reacción se calentó a 85ºC en un tubo cerrado herméticamente durante 12 horas.

La reacción se repartió entre H_2O y $CHCl_3$, la capa orgánica se secó con Na_2SO_4, se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 35-50%/Hexanos), produciendo el compuesto del título en forma de un sólido de color amarillo (61 mg, 28%): LC-MS (ES) m/z = 521.

b) *N*-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tiofenocarboxamida

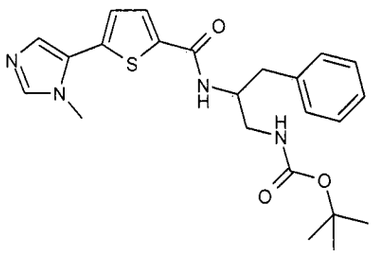
Se añadió HCl en dioxano (4 M, 1 ml) a una solución de [2-({[5-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (61 mg, 0,12 mmol) en $CHCl_3$/MeOH (10:1, 10 ml) y la mezcla se agitó durante una noche. Después de que se completara, la mezcla se absorbió sobre gel de sílice y se purificó por cromatografía (90:10:1 de $CHCl_3$/MeOH/NH_4OH). El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título en forma de un sólido de color blanco (30 mg, 0,09 mmol, 77%): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,79 - 2,91 (m, 3 H) 2,94 (t, *J* = 5,56 Hz, 1 H) 4,10 (s, 3 H) 4,25 - 4,34 (m, 1 H) 7,18 (ddd, *J* = 8,27, 5,75, 3,16 Hz, 1 H) 7,24 - 7,29 (m, 4 H) 7,63 (d, *J* = 4,04 Hz, 1 H) 7,75 (d, *J* = 4,04 Hz, 1 H) 7,95 (s, 1 H).

Ejemplo 62



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-imidazol-5-il)-2-tiofenocarboxamida

a) [2-({[5-(1-metil-1*H*-imidazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



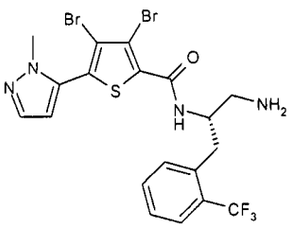
A una solución de [2-fenil-2-({[5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-2-tienil]carbonil}amino)etil]carbamato de 1,1-dimetiletilo (72 mg, 0,15 mmol) [preparada de acuerdo con el procedimiento del Ejemplo 3] en dioxano/H_2O (5:1, 1,4 ml) se le añadieron Cs_2CO_3 (200 mg, 0,61 mmol), tetraquistrifenilfosfina Pd(0) (8,5 mg, 0,01 mmol) y 5-bromo-1-metil-1*H*-imidazol (64 mg, 0,40 mmol). La mezcla de reacción se calentó a 85°C en un tubo cerrado herméticamente durante 12 h. Después de que se completara, la mezcla de reacción se repartió entre H_2O (25 ml) y $CHCl_3$. Los extractos orgánicos se secaron (Na_2SO_4), se concentraron al vacío, se absorbieron sobre gel de sílice y se purificaron por cromatografía en columna (EtOAc al 35 – 50%/Hexanos) para dar el compuesto del título (19,6 mg, 31%) en forma de un sólido de color amarillo: LC-MS (ES) m/z = 441.

b) *N*-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-imidazol-5-il)-2-tiofenocarboxamida

Se añadió HCl en dioxano (4 M, 1 ml) a una solución de [2-({[5-(1-metil-1*H*-imidazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (19,6 mg, 0,04 mmol) en $CHCl_3$/MeOH (10:1, 5 ml). Después de que se completara la reacción, la mezcla se absorbió sobre gel de sílice y se purificó por cromatografía (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título en forma de un sólido de color blanco (19 mg, 0,05 mmol, cuant.): LC-MS (ES) m/z 341 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 2,77 - 2,83 (m, 1 H) 2,85 - 2,91 (m, 2 H) 2,93 - 2,99 (m, 1 H) 3,82 (s, 3 H) 4,30 (ddd, *J* = 8,08, 4,80, 1,77 Hz, 1 H) 7,15 - 7,31 (m, 7 H) 7,69 (d, *J* = 4,04 Hz, 1 H) 7,76 (s, 1 H).

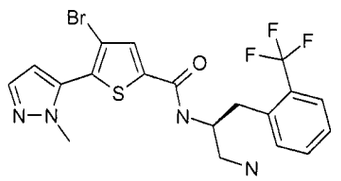
Ejemplo 63:



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (253 mg, 0,69 mmol). La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice, MeOH al 3% en DCM (NH_4OH al 1%)), produciendo el compuesto del título, que se purificó adicionalmente por cromatografía de fase inversa Gilson con H_2O al 5-95% (TFA al 1%)/MeCN (TFA al 1%) para producir la sal TFA: LC-MS (ES) m/z 569 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,14 - 3,30 (m, 4 H) 3,82 (s, 3 H) 4,73 (dd, *J* = 9,47, 4,67 Hz, 1 H) 6,54 (d, *J* = 2,02 Hz, 1 H) 7,44 - 7,50 (m, 1 H) 7,56 - 7,62 (m, 3 H) 7,74 (d, *J* = 7,83 Hz, 1 H).

Ejemplo 64:

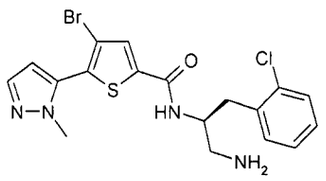


Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (143 mg, 0,50 mmol): LC-MS (ES) m/z 488 $(M+H)^+$, ^1H RMN (400

MHz, MeOD) ppm 3,15 (s, 2 H) 3,23 (s, 2 H) 3,84 (s, 3 H) 4,65 (s, 1 H) 6,52 - 6,57 (m, 1 H) 7,46 (s, 1 H) 7,52 - 7,61 (m, 3 H) 7,72 (s, 1 H) 7,81 (s, 1 H).

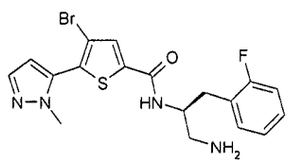
Ejemplo 65



Preparación de *N*-{(1*S*)-2-amino-1-[(2-clorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (143 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(2-clorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona-HCl (157 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 455 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) ppm 3,11 (s, 1 H) 3,22 (s, 1 H) 3,27 (s, 2 H) 3,85 (s, 3 H) 4,70 (s, 1 H) 6,57 (s, 1 H) 7,26 (s, 2 H) 7,41 (s, 2 H) 7,66 (s, 1 H) 7,88 (s, 1 H).

Ejemplo 66

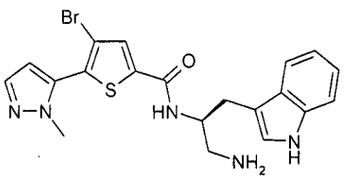


Preparación de *N*-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo claro de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se

sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (143 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(2-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona-HCl (149 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 438 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,00 (s, 1 H) 3,09 (s, 1 H) 3,15 (dd, J = 3,41, 1,64 Hz, 2 H) 3,83 (s, 4 H) 4,58 (s, 1 H) 6,52 (d, J = 2,02 Hz, 1 H) 7,08 - 7,17 (m, 3 H) 7,27 - 7,37 (m, 3 H) 7,59 (d, J = 2,02 Hz, 1 H) 7,74 (d, J = 3,54 Hz, 1 H).

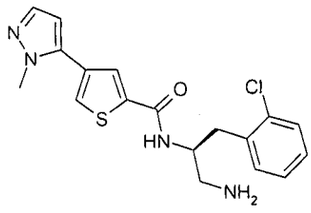
Ejemplo 67:



Preparación de *N*-[(1*S*)-2-amino-1-(1*H*-indol-3-ilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-tiofenocarboxílico (143 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(1*H*-indol-3-il)propil]-1*H*-isoindolo-1,3(2*H*)-diona-diona-HCl (160 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 459 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,15 (dt, J = 10,42, 6,79 Hz, 3 H) 3,27 (dd, J = 4,04, 2,27 Hz, 1 H) 3,84 (s, 3 H) 4,63 (d, J = 6,82 Hz, 1 H) 6,54 (d, J = 2,02 Hz, 1 H) 7,05 (t, J = 7,45 Hz, 1 H) 7,13 (t, J = 7,07 Hz, 1 H) 7,19 (s, 1 H) 7,37 (d, J = 8,08 Hz, 1 H) 7,64 - 7,73 (m, 2 H) 7,77 (s, 1 H).

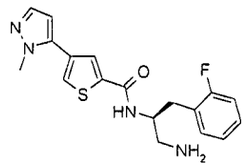
Ejemplo 68:



Preparación de *N*-{(1*S*)-2-amino-1-[(2-clorofenil)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(2-clorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona-HCl (157 mg, 0,5 mmol) [preparada de acuerdo con la Preparación 6]: LC-MS (ES) m/z 375 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) ppm 3,11 - 3,20 (m, 1 H) 3,22 - 3,31 (m, 3 H) 4,23 (s, 3 H) 4,75 (s, 1 H) 6,96 (s, 1 H) 7,18 - 7,26 (m, 2 H) 7,38 (d, J = 6,06 Hz, 1 H) 7,46 (d, J = 4,55 Hz, 1 H) 8,22 (s, 2 H) 8,32 (s, 1 H).

Ejemplo 69

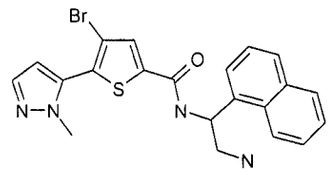


Preparación de *N*-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(2-fluorofenil)propil]-1*H*-

isoindolo-1,3(2*H*)-diona-HCl (149 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 359 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,06 - 3,17 (m, 2 H) 3,25 - 3,31 (m, 2 H) 4,18 (s, 3 H) 4,59 - 4,67 (m, 1 H) 6,88 (s, 1 H) 7,05 - 7,12 (m, 2 H) 7,23 - 7,30 (m, 1 H) 7,36 - 7,42 (m, 1 H) 8,12 (d, J = 1,01 Hz, 1 H) 8,17 (s, 1 H) 8,21 (s, 1 H).

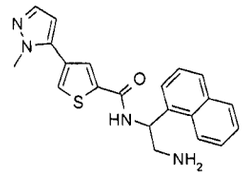
Ejemplo 70



Preparación de *N*-[2-amino-1-(1-naftalenil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por [2-amino-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo (143 mg, 0,5 mmol) [de la Preparación 16]: LC-MS (ES) m/z 456 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,60 (s, 1 H) 3,72 (s, 1 H) 3,84 (s, 3 H) 6,33 (d, J = 10,11 Hz, 1 H) 6,55 (s, 1 H) 7,55 - 7,61 (m, 3 H) 7,64 (d, J = 8,34 Hz, 1 H) 7,74 (s, 1 H) 7,92 - 7,99 (m, 2 H) 8,09 (s, 1 H) 8,26 (s, 1 H).

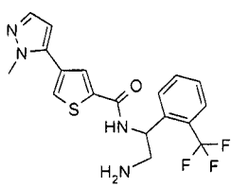
Ejemplo 71:



Preparación de *N*-[2-amino-1-(1-naftalenil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó ácido 4,5-dibromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por [2-amino-2-(1-naftalenil)etil]carbamato de 1,1-dimetiletilo (143 mg, 0,5 mmol) [de la Preparación 16]: LC-MS (ES) m/z 377 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,62 (d, J = 4,04 Hz, 1 H) 3,67 - 3,78 (m, 1 H) 4,08 - 4,10 (m, 3 H) 6,35 (s, 1 H) 6,73 (d, J = 2,27 Hz, 1 H) 7,55 - 7,60 (m, 2 H) 7,62 - 7,67 (m, 1 H) 7,76 (d, J = 7,33 Hz, 1 H) 7,88 (d, J = 2,53 Hz, 1 H) 7,93 - 7,99 (m, 2 H) 8,10 (d, J = 1,52 Hz, 1 H) 8,23 - 8,27 (m, 2 H).

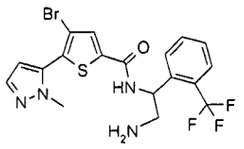
Ejemplo 72



Preparación de *N*-{2-amino-1-[2-(trifluorometil)fenil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó ácido 4,5-dibromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por {2-amino-2-[2-(trifluorometil)fenil]etil}carbamato de 1,1-dimetiletilo (152 mg, 0,5 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,36 - 3,39 (m, 1 H) 3,46 - 3,53 (m, 1 H) 3,98 (s, 3 H) 5,86 - 5,91 (m, 1 H) 6,48 (s, 1 H) 7,51 (d, J = 2,02 Hz, 1 H) 7,60 (s, 1 H) 7,76 (s, 1 H) 7,83 (d, J = 8,08 Hz, 2 H) 7,94 (s, 1 H) 8,05 (s, 1 H).

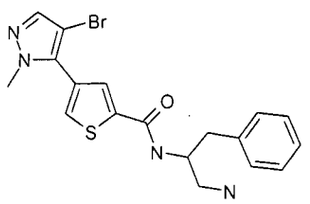
Ejemplo 73



Preparación de *N*-{2-amino-1-[2-(trifluorometil)fenil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por {2-amino-2-[2-(trifluorometil)fenil]etil}carbamato de 1,1-dimetiletilo (152 mg, 0,5 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z 474 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,37 (s, 1 H) 3,65 (s, 1 H) 3,89 - 4,00 (m, 3 H) 5,88 (s, 1 H) 6,76 (d, J = 2,27 Hz, 1 H) 7,58 (s, 1 H) 7,77 (d, J = 9,60 Hz, 2 H) 7,91 - 8,03 (m, 2 H) 8,26 (d, J = 2,27 Hz, 1 H).

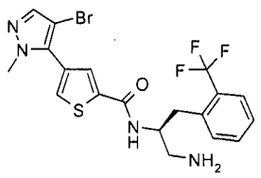
Ejemplo 74



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 24, con la excepción de que se sustituyó NCS por NBS (194 mg, 1,09 mmol): LC-MS (ES) m/z 418 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,03 (d, J = 7,33 Hz, 2 H) 3,23 (s, 2 H) 3,90 (s, 3 H) 4,56 (d, J = 1,77 Hz, 1 H) 7,20 - 7,27 (m, 1 H) 7,28 - 7,34 (m, 4 H) 7,58 (s, 1 H) 7,96 (s, 2 H).

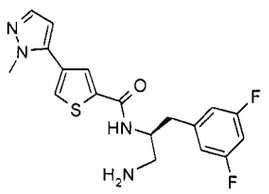
Ejemplo 75



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 25, con la excepción de que se sustituyó NCS por NBS (67 mg, 0,5 mmol): LC-MS (ES) m/z 488 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) ppm 3,10 - 3,19 (m, 1 H) 3,20 - 3,28 (m, 3 H) 3,91 (s, 3 H) 4,66 (dd, J = 8,59, 3,03 Hz, 1 H) 7,39 - 7,47 (m, 1 H) 7,51 - 7,58 (m, 2 H) 7,59 (s, 1 H) 7,72 (d, J = 8,08 Hz, 1 H) 7,98 (s, 2 H).

Ejemplo 76

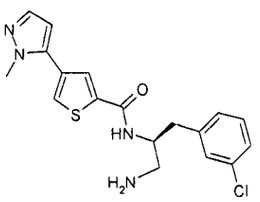


Preparación de *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo claro de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona-HCl (158 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H RMN (400 MHz, DMSO) ppm 2,94 - 3,06 (m, 4 H) 3,95 (s, 3 H) 4,40 (d, J = 6,06 Hz, 1 H) 6,46

(d, J = 1,77 Hz, 1 H) 7,00 - 7,10 (m, 3 H) 7,47 (d, J = 1,77 Hz, 1 H) 7,99 (d, J = 1,26 Hz, 1 H) 8,10 (s, 2 H) 8,21 (s, 1H) 8,92 (d, J = 8,0 Hz, 1H).

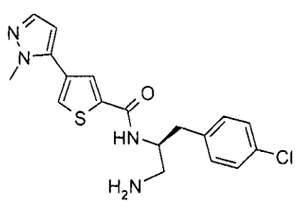
Ejemplo 77



Preparación de *N*-{(1*S*)-2-amino-1-[(3-clorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(3-clorofenil)propil]-*1H*-isoindolo-1,3(2*H*)-diona (157 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H RMN (400 MHz, DMSO) ppm 2,92 - 3,04 (m, 4 H) 3,92 - 3,98 (m, 3 H) 4,36 (d, J = 5,56 Hz, 1 H) 6,47 (s, 1H) 7,19 - 7,29 (m, 2 H) 7,29 - 7,35 (m, 1 H) 7,37 - 7,42 (m, 1 H) 7,47 (s, 1H) 8,17 (s, 3 H) 8,85-9,07 (m, 1H).

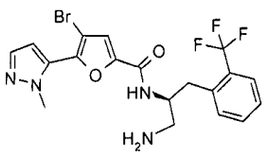
Ejemplo 78:



Preparación de *N*-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (104 mg, 0,5 mmol) y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona-HCl por 2-[(2*S*)-2-amino-3-(4-clorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (157 mg, 0,5 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 395 $(M+H)^+$, ^1H RMN (400 MHz, DMSO) ppm 2,92 - 2,97 (m, 2 H) 2,99 - 3,04 (m, 2 H) 4,01 (s, 3 H) 4,32 - 4,42 (m, 1 H) 6,43 - 6,50 (m, 1 H) 7,27 - 7,37 (m, 4 H) 7,47 (d, J = 1,77 Hz, 1 H) 7,99 (d, J = 1,26 Hz, 1 H) 8,21 (s, 3 H) 8,94-9,10 (m, 1H).

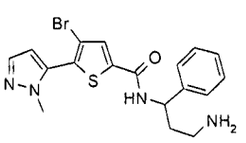
Ejemplo 79



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4,5-dibromo-2-furanocarboxílico (135 mg, 0,5 mmol): LC-MS (ES) m/z 472 $(M+H)^+$, ^1H RMN (400 MHz, DMSO) ppm 3,11 (d, J = 9,85 Hz, 1 H) 3,21 - 3,31 (m, 3 H) 4,06 (s, 3 H) 4,70 (s, 1 H) 6,87 (d, J = 2,02 Hz, 1 H) 7,33 (s, 1 H) 7,41 - 7,48 (m, 1 H) 7,50 - 7,57 (m, 2 H) 7,60 (d, J = 2,02 Hz, 1 H) 7,71 (d, J = 7,83 Hz, 1 H).

Ejemplo 80

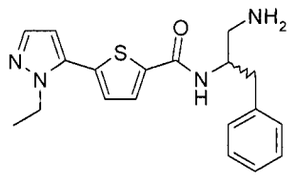


Preparación de *N*-(3-amino-1-fenilpropil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

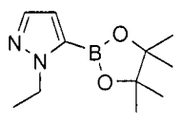
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por [3-(metilamino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (125 mg, 0,5 mmol) [de la Preparación 3]: LC-MS (ES) m/z 420 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO) ppm 2,25 - 2,37 (m, 2 H) 2,96 (d, J = 8,08 Hz, 1 H) 3,04 - 3,13 (m, 1 H) 3,84 (s, 3 H) 5,22 (t, J = 7,58 Hz, 1 H) 6,53 (d, J = 1,52 Hz, 1 H) 7,35 (d, J = 6,57 Hz, 1 H) 7,44 (dt, J = 15,09, 7,48 Hz, 4 H) 7,58,

Ejemplo 81

Preparación de *N*-[2-amino-1-(fenilmetil)etil]-5-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



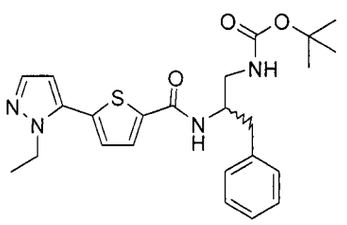
a) 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol



A una suspensión de NaH (al 60% en aceite mineral, 2,2 g, 55 mmol) en THF (50 ml) se le añadió pirazol (3,4 g, 50 mmol) en THF (10 ml) a temperatura ambiente. Después de 30 min, a la suspensión anterior se le añadió gota a gota EtI (7,75 g, 50 mmol). Después de que se completara la reacción (20 h), la suspensión se filtró y la solución resultante se usó directamente con purificación adicional.

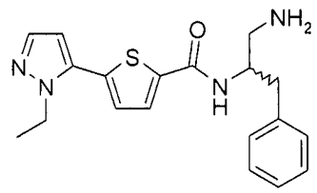
A 0°C, a la solución anterior de 4-metil pirazol (~50 mmol) se le añadió n-BuLi (2,5 M en hexano, 22 ml, 55 mmol). La solución de reacción se agitó durante 1 hora a TA y después se enfrió a -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. A la solución de reacción se le añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (10,2 g, 55 mmol). Después de 15 min a -78°C, la reacción se dejó calentar a 0°C durante 1 hora. La reacción se diluyó con una solución saturada de NH_4Cl y se extrajo con DCM. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío para producir un sólido de color castaño (9,8 g, 89%) que se usó sin purificación adicional. LCMS (ES) m/z 141 $(M+H)^+$ para $[RB(OH)_2]$; ^1H RMN ($CDCl_3$, 400 MHz) ppm 7,52 (d, J = 2 Hz, 1H), 6,36 (d, J = 2 Hz, 1H), 4,48 (c, J = 7,2 Hz, 2H), 1,44 (t, J = 7,2 Hz, 3H), 1,36 (s, 12 H)

b) [2-({[5-(1-etil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



A una solución de (2-{[(5-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (100 mg, 0,23 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (100 mg, 0,72 mmol), tetraquistrifenilfosfina Pd(0) (30 mg, 26 μmol) y 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (64 mg, 0,29 mmol). La mezcla de reacción se calentó a 78°C en un tubo cerrado herméticamente. Después de 12 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (hex/EtOAc, 40-60%) para producir el compuesto del título (0,074 g, 71%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z 455 $(M+H)^+$.

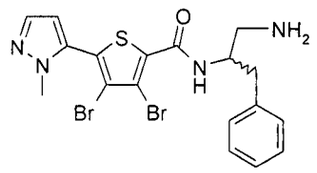
c) *N*-[2-amino-1-(fenilmetil)etil]-5-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



Se disolvió [2-({[5-(1-etil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (74 mg, 0,16 mmol) en DCM (2 ml) y se trató con TFA (1 ml). Después de 1 h, la solución se concentró y se neutralizó a través de sílice usando MeOH al 4% en DCM (NH_4OH al 1%). El compuesto del título se purificó adicionalmente usando HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40-10%), produciendo la sal bis-TFA del compuesto del título (47 mg, 50%) en forma de un sólido de color blanco: LCMS (ES) m/z 355 $(M+H)^+$, ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,71 (d, J = 3,8 Hz, 1H), 7,55 (d, J = 2,0 Hz, 1H), 7,34-7,22 (m, 6H), 6,51 (d, J = 1,8 Hz, 1H), 4,55 (m, 1H), 4,34 (c, J = 7,1 Hz, 2H), 3,22 (dd, J = 3,5, 13,1 Hz, 1H), 3,13 (dd, J = 10,1, 13,1 Hz, 1H), 3,00 (m, 2H) y 1,42 (t, J = 7,1 Hz, 3H).

Ejemplo 82

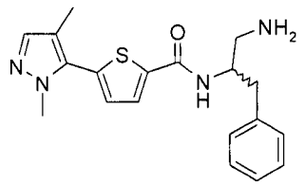
Preparación de *N*-[2-amino-1-(fenilmetil)etil]-3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se sustituyó [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por (3-fenil-2-{[(3,4,5-tribromo-2-tienil)carbonil]amino}propil)carbamato de 1,1-dimetiletilo (120 mg, 0,20 mmol): LC-MS (ES) m/z 499 $(M+H)^+$, ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,59 (d, J = 2,0 Hz, 1H), 7,37-7,24 (m, 5H), 6,53 (d, J = 2,0 Hz, 1H), 4,62 (m, 1H), 3,27 (d, J = 13,1, 4,3 Hz, 1H), 3,21 (dd, J = 13,1, 9,4 Hz, 1H), 3,09 (dd, J = 14,2, 6,1 Hz, 1H), 3,02 (dd, J = 13,9, 9,1 Hz, 1H) y 1,96 (s, 3H).

Ejemplo 83

N-[2-amino-1-(fenilmetil)etil]-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

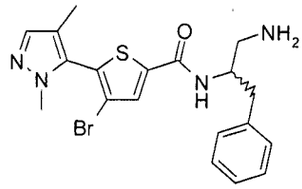


a) *N*-[2-amino-1-(fenilmetil)etil]-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se sustituyó 1,1-dimetiletilo [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanil]carbonil}amino)-3-fenilpropil]carbamato por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (64,0 mg, 0,23 mmol) [de la Preparación 17] y se sustituyó (2-{[(5-bromo-3-tienil)carbonil]amino}-2-feniletil)carbamato de 1,1-dimetiletilo por (2-{[(5-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (110 mg, 0,25 mmol): LC-MS (ES) m/z 355 $(M+H)^+$, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 7,75 (d, J = 3,8 Hz, 1H), 7,40 (s a, 1H), 7,32-7,23 (m, 5H), 7,21 (d, J = 3,8 Hz, 1H), 4,56 (m, 1H), 3,86 (s, 3H), 3,23 (dd, J = 13,1, 3,8 Hz, 1H), 3,15 (dd, J = 12,9, 10,1 Hz, 1H), 3,01 (m, 2H) y 2,10 (s, 3H).

Ejemplo 84

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

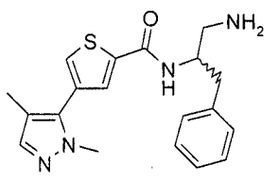


El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se

sustituyó 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (77 mg, 0,23 mmol) [de la Preparación 17] y se sustituyó [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por (2-{[(4,5-dibromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (150 mg, 0,29 mmol): LC-MS (ES) m/z 434 $(M+H)^+$, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 7,77 (s, 1H), 7,43 (s, 1H), 7,35-7,23 (m, 5H), 4,55 (m, 1H), 3,72 (s, 3H), 3,23 (dd, J = 3,5 Hz, 1H), 3,13 (dd, J = 10,6, 13,1 Hz, 1H), 3,02 -2,95 (m, 2H) y 1,99 (s, 3H).

Ejemplo 85

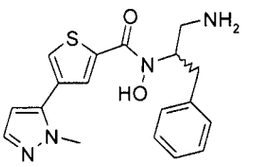
N-[2-amino-1-(fenilmetil)etil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



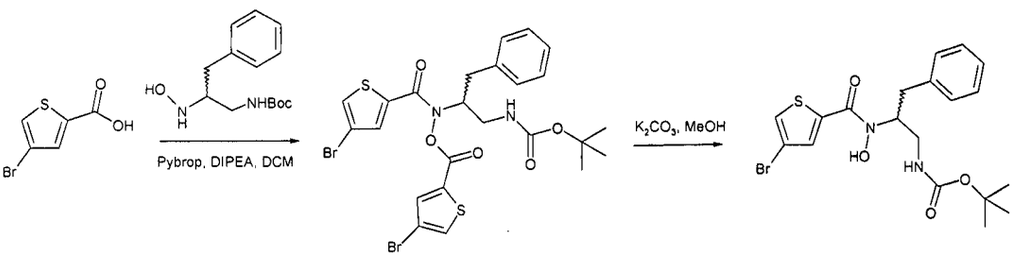
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 1, con la excepción de que se sustituyó 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (220 mg, 1,0 mmol) [de la Preparación 17] y se sustituyó [2-({[4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por (2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (150 mg, 0,34 mmol): LC-MS (ES) m/z = 355 $(M+H)^+$, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 8,14-8,13 (m, 3H), 7,35-7,20 (m, 5H), 4,58 (m, 1H), 4,07 (s, 3H), 3,36-3,22 (m, 2H), 3,12-3,01 (m, 2H) y 2,21 (s, 3H).

Ejemplo 86

N-[2-amino-1-(fenilmetil)etil]-*N*-hidroxi-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



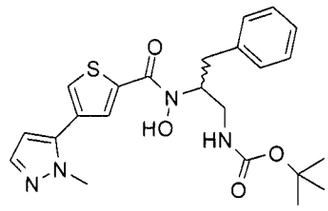
a) {2-[[(4-bromo-2-tienil)carbonil](hidroxi)amino]-3-fenilpropil}carbamato de 1,1-dimetiletilo



A una solución de ácido 4-bromo-2-tiofenocarboxílico (1,0 g, 4,83 mmol) en DCM (10 ml) se le añadieron PyBrop (3,4 g, 7,24 mmol) y base de Hunig (2 ml, 12,6 mmol). Después de 15 min, a la mezcla de reacción se le añadió [2-(hidroxiamino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (641 mg, 2,41 mmol) en DCM (2 ml) y se agitó durante 2 h a TA. La solución de reacción se concentró para dar el [2-([(4-bromo-2-tienil)carbonil]{[(4-bromo-2-tienil)carbonil]oxi}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo bruto. LC-MS (ES) m/z = 645 $(M+H)^+$.

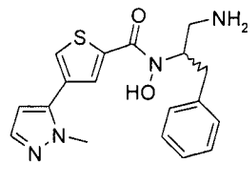
A una solución de [2-([(4-bromo-2-tienil)carbonil]{[(4-bromo-2-tienil)carbonil]oxi}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo en MeOH (5 ml) se le añadió K_2CO_3 (1,0 g, 7,3 mmol). La mezcla se agitó a TA durante 2 h. La mezcla se concentró al vacío y se purificó sobre gel de sílice (EtOAc/Hexano, 30%) para dar el compuesto del título (410 mg, 37% en dos etapas) en forma de un sólido de color blanquecino: LC-MS (ES) m/z = 456 $(M+H)^+$.

b) [2-(hidroxi{[4-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



A una solución de {2-[[(4-bromo-2-tienil)carbonil](hidroxi)amino]-3-fenilpropil}carbamato de 1,1-dimetiletilo (100 mg, 0,22 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (91 mg, 0,66 mmol), tetraquistrifenilfosfina Pd(0) (23 mg, 0,022 mmol) y 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (68 mg, 0,33 mmol). La mezcla de reacción se calentó a 75°C en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (EtOAc/Hex, 20-40%) para producir el compuesto del título (87 mg, 87%): LC-MS (ES) m/z = 456 $(M+H)^+$.

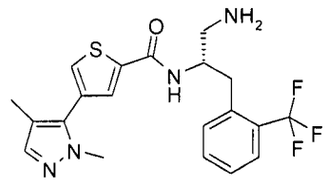
c) *N*-[2-amino-1-(fenilmetil)etil]-*N*-hidroxi-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



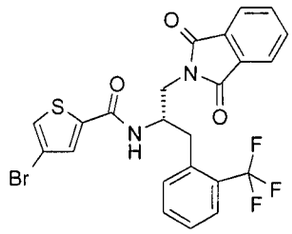
Se disolvió [2-(hidroxi{[4-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (84 mg, 0,19 mmol) en DCM (2 ml) y la mezcla se trató con TFA (1 ml). La reacción se agitó durante 1 h, se concentró, se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40 -10%) y se concentró para producir la sal bis-TFA del compuesto del título (51,2 mg, 64,8%). LC-MS (ES) m/z 357 $(M+H)^+$, ^1H RMN (d_4-MeOD, 400 MHz) ppm 8,03 (s, 1H), 7,94 (d, J = 1,8 Hz, 1H), 7,52 (d, J = 1,8 Hz, 1H), 6,46 (d, J = 1,8 Hz, 1H), 7,34-7,18 (m, 5H), 5,16 (m, 1H), 3,95 (s, 3H), 3,38 (dd, J = 13,1, 10,6 Hz, 1H), 3,17-3,11 (m, 2H) y 2,95 (dd, J = 13,6, 6,6 Hz, 1H)

Ejemplo 87

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

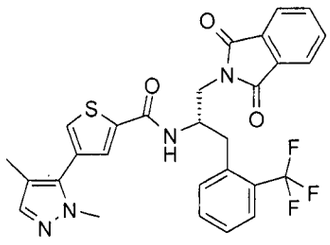


a) 4-bromo-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



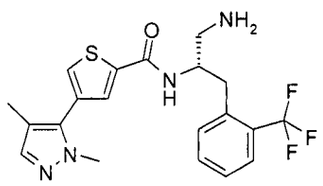
A una solución de ácido 4-bromo-2-tiofenocarboxílico (80 mg, 0,39 mmol) en DCM (2 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (218 mg, 0,47 mmol), seguido de la adición de DIPEA (0,2 ml, 1,14 mmol). Después de agitar durante 10 min, a la solución anterior se le añadió la diamina 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (165 mg, 0,43 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, MeOH al 10% en CH_3Cl), produciendo el compuesto del título (206 mg, 99%) en forma de un sólido de color blanco: LC-MS (ES) m/z 538 $(M+H)^+$.

b) 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de 4-bromo-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (200 mg, 0,37 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (0,17 g, 1,23 mmol), tetraquistrifenilfosfina Pd(0) (42 mg, 0,036 mmol) y 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (413 mg, 1,86 mmol) [de la Preparación 17]. La mezcla de reacción se calentó a 88°C en un tubo cerrado herméticamente durante 2 h. La solución de reacción se concentró al vacío y se purificó sobre gel de sílice (EtOAc al 10-50%/Hex) para dar el compuesto del título (192 mg, 94%) en forma de un sólido de color blanco: LC-MS (ES) m/z 553 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

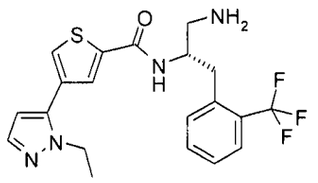


Se disolvió 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (110 mg, 0,198 mmol) en MeOH (2 ml) y la mezcla se trató con NH_2NH_2 (0,5 ml, 15,93 mmol). La reacción se agitó durante 10 h, se concentró y el residuo en DCM (2 ml) se trató con TFA (1,0 ml). Después de agitar durante 2 h, el disolvente se retiró y el residuo se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40-10%) y se concentró para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se neutralizó a través de un lecho de sílice (90:9:1 de $CHCl_3$/MeOH/NH_4OH), produciendo la base libre del compuesto del título. Después, la base libre, en forma

de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (62 mg, 34,6%) en forma de la sal HCl: LC-MS (ES) m/z 423 $(M+H)^+$, ^1H RMN (d4-MeOD, 400 MHz) ppm 8,27 (s, 1H), 8,22 (s, 1H), 8,18 (s, 1H), 7,70 (d, 7,8 Hz, 1H), 7,64 (d, J = 7,6 Hz, 1H), 7,51 (dd, J = 7,3, 7,3 Hz, 1H), 7,41 (dd, J = 7,6, 7,3 Hz, 1H), 4,69 (m, 1H), 4,12 (s, 3H), 3,41-3,19 (m, 4H) y 2,24 (s, 3H).

Ejemplo 88

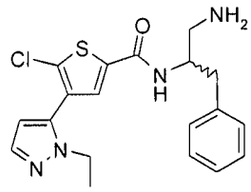
N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-1H-pirazol-5-il)-2-tiofenocarboxamida



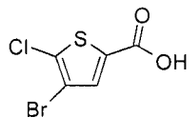
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 87, con la excepción de que se sustituyó 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol por 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (104 mg, 0,47 mmol). LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H RMN (d_4-MeOD, 400 MHz) ppm 8,35-8,31 (m, 2H), 8,21 (s a, 1H), 7,70 (d, J = 7,8 Hz, 1H), 7,64 (d, J = 7,3 Hz, 1H), 7,51 (dd, J = 7,3, 7,3 Hz, 1H), 7,42 (dd J = 7,6, 7,3 Hz, 1H), 7,00 (m, 1H), 4,70-4,61 (m, 3H), 3,40-3,17 (m, 4H) y 1,57 (t, J = 6,8 Hz, 3H).

Ejemplo 89

N-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

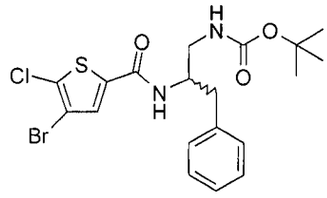


a) ácido 5-cloro-4-metil-2-tiofenocarboxílico



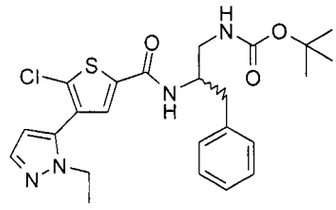
A una solución de ácido 4-bromo-2-tiofenocarboxílico (2,07 g, 10 mmol) en DMF (5 ml) se le añadió en una porción NCS (2,7 g, 15 mmol). La mezcla de reacción se agitó a 50°C durante 10 h y después se enfrió a temperatura ambiente. El producto deseado precipitó después de que se añadiera agua (5 ml). El sólido blanco se filtró y se secó a alto vacío para dar 1,9 g (79%). LC-MS (ES) m/z = 242 $(M+H)^+$.

b) (2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo



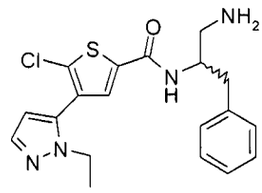
A una solución de ácido 5-cloro-4-metil-2-tiofenocarboxílico (242 mg, 1,0 mmol) y diisopropiletil amina (2,5 ml, 14,60 mmol) en DCM (50 ml) a 25°C se le añadió en una porción PyBrOP (2,5 g, 5,30 mmol). Después de 30 min, se añadió en una porción (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (250 mg, 1,0 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 10-40% en hexano), produciendo el compuesto del título (460 mg, 97%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 474 $(M+H)^+$.

c) [2-({[5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



A una solución de (2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (100 mg, 0,21 mmol) en THF (5 ml) se le añadieron Na_2CO_3 (2 N, 0,3 ml, 0,6 mmol), $Pd(dppf)Cl_2$ (20 mg, 24 μmol) y 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (92 mg, 0,42 mmol). La mezcla de reacción se calentó a 80ºC en un tubo cerrado herméticamente en una atmósfera de N_2. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (hex/EtOAc, 20-50%) para producir el compuesto del título (74 mg, 72%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z 489 $(M+H)^+$.

d) *N*-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

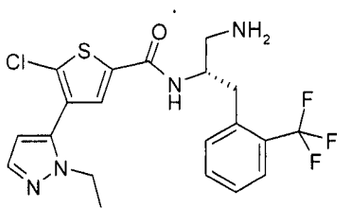


Se disolvió [2-({[5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (61 mg, 0,12 mmol) en DCM (2 ml) y la mezcla se trató con TFA (1 ml). Después de 0,5 h, la solución se concentró y se neutralizó a través de sílice usando MeOH al 4% en DCM (NH_4OH al 1%). El compuesto del título se purificó adicionalmente usando HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40-10%), produciendo la sal bis-TFA del compuesto del título (41 mg, 53%) en forma de un sólido de color blanco. LC-MS (ES) m/z =

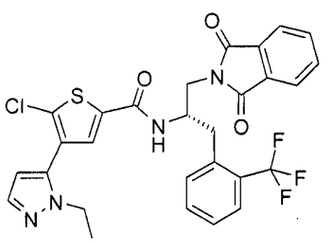
389 $(M+H)^+$. ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,61 (d, J = 2,0 Hz, 1H), 7,59 (s, 1H), 7,33-7,21 (m, 5H), 6,41 (d, J = 2,0 Hz, 1H), 4,52 (m, 1H), 4,10 (c, J = 7,1 Hz, 2H), 3,22 (dd, J = 12,9, 3,5 Hz, 1H), 3,12 (dd, J = 12,6, 10,1 Hz, 1H), 2,98 (m, 2H) y 1,35 (t, J = 7,1 Hz, 3H).

Ejemplo 90

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

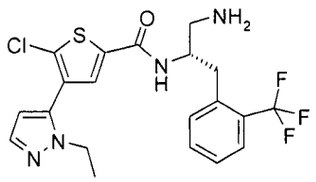


a) 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 89(c), con la excepción de que se sustituyó (2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por 4-bromo-5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (150 mg, 0,26 mmol): LC-MS (ES) m/z 587 $(M+H)^+$.

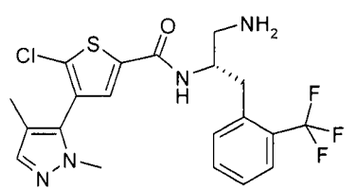
b) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



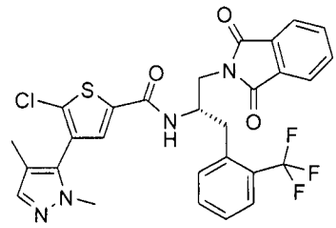
A una solución de 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (110 mg, 0,19 mmol) en MeOH/THF (5 ml/0,5 ml) se le añadió hidrazina (0,5 ml, 15,9 mmol). Después de agitar durante una noche a TA, la mezcla de reacción se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40-10%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se neutralizó con hidróxido de amonio. La mezcla se extrajo con DCM (5 ml x 3), se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título, que se disolvió en MeOH (2 ml) y se trató con HCl (ac., 37%). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (26 mg, 26%) en forma de una sal di-HCl: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H RMN (d_4-MeOD, 400 MHz) ppm 8,28 (d, J = 2,5 Hz, 1H), 8,07 (s, 1H), 7,70 (d, J = 7,6 Hz, 1H), 7,62 (d, J = 7,6 Hz, 1H), 7,53 (dd, J = 7,3, 7,6 Hz, 1H), 7,43 (dd, J = 7,6, 7,6 Hz, 1H), 6,90 (d, J = 2,5 Hz, 1H), 4,66 (m, 1H), 4,43 (c, J = 7,3 Hz, 2H), 3,37-3,16 (m, 4H) y 1,50 (t, J = 7,3 Hz, 3H).

Ejemplo 91

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

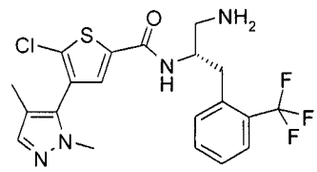


a) 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de 4-bromo-5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (260 mg, 0,46 mmol) en THF (5 ml) se le añadieron Na_2CO_3 (2 N, 0,7 ml, 1,4 mmol), $Pd(dppf)Cl_2$ (40 mg, 48 μmol) y 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (303 mg, 1,38 mmol). La mezcla de reacción se calentó a 75ºC en un tubo cerrado herméticamente en una atmósfera de N_2. Después de 8 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (10:1 de CHCl3/MeOH) para producir el compuesto del título (196 mg, 73,4%): LC-MS (ES) m/z = 587 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

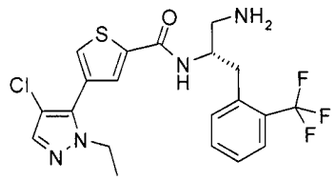


A una solución de 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (196 mg, 0,34 mmol) en MeOH/THF (2 ml/0,5 ml) se le añadió hidrazina (0,5 ml, 15,9 mmol). Después de agitar durante una noche a TA, la mezcla de reacción se concentró y se purificó sobre sílice (MeOH al 50% en $CHCl_3$ (0,5% NH_4OH) para dar una base libre del compuesto del título, que se disolvió en MeOH (2 ml), y se trató con HCl (ac., 37%). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (107 mg, 51%) en forma de una sal di-HCl: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,96 (s, 1H), 7,90 (m, 1H), 7,70 (d, J = 7,6 Hz, 1H), 7,60 (d, J = 7,6 Hz, 1H), 7,53 (t,

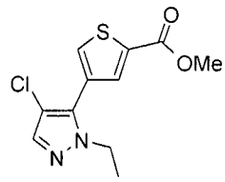
J = 7,3 Hz, 1H), 7,43 (t, J = 7,3 Hz, 1H), 4,66 (m, 1H), 3,91 (s, 3H), 3,33-3,14 (m, 4H) y 2,10 (s, 3H).

Ejemplo 92

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



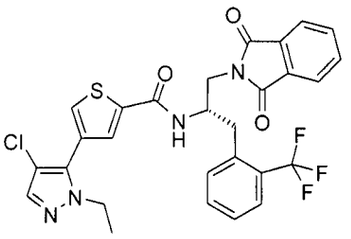
a) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 4-bromo-2-tiofenocarboxilato de metilo (1,0 g, 4,52 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (1,86 g, 13,5 mmol), tetraquistrifenilfosfina Pd(0) (260 mg, 0,23 mmol) y 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol(1,3 g, 5,85 mmol). La mezcla de reacción se calentó a 78ºC en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (hex/EtOAc, 20-40%) para producir 4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (0,7 g, 66%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z = 237 $(M+H)^+$.

A una solución del compuesto anterior (0,5 g, 2,11 mmol) en THF (10 ml) se le añadió NCS (0,364 g, 2,74 mmol). La mezcla de reacción se calentó a 78ºC en una atmósfera de nitrógeno. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (Hexanos/EtOAc, 10-20%) para producir el compuesto del título (0,45 g, 78%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z 271 $(M+H)^+$.

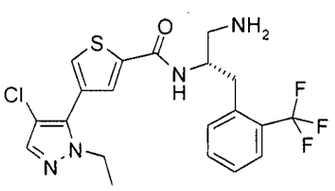
(b) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (0,3 g, 1,1 mmol) en THF/H_2O (5 ml/0,5 ml) se le añadió KOH (0,2 g, 3,4 mmol). La mezcla de reacción se calentó a 58°C durante 4 h y después se concentró y se diluyó con H_2O (2 ml). El valor del pH se ajustó a 3 con HCl acuoso. La mezcla se extrajo con DCM (3 x 5 ml) y las fracciones orgánicas recogidas se concentraron al vacío para dar el ácido 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxílico bruto (260 mg) que se usó directamente sin purificación adicional. LC-MS (ES) m/z = 256 $(M+H)^+$.

A una solución de ácido 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (0,26 g, 1,0 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (0,35 g, 1,1 mmol) y DIPEA (0,5 ml, 2,86 mmol) en DCM (5 ml) a 25°C se le añadió en una porción PyBrOP (0,6 g, 1,2 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/hexano), produciendo el compuesto del título (0,54 g, 91%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 588 $(M+H)^+$.

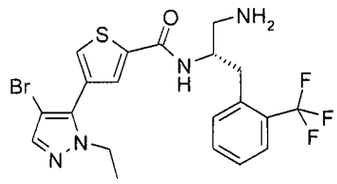
c) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



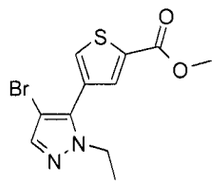
Se disolvió 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (350 mg, 0,60 mmol) en MeOH (5 ml) y la mezcla se trató con NH_2NH_2 (0,5 ml,15,93 mmol). La mezcla se agitó a TA durante una noche y se concentró. El residuo se purificó por cromatografía en columna (sílice, MeOH al 2-5% en $CHCl_3$ (NH_4OH al 0,5%), produciendo la base libre del compuesto del título, que se trató con HCl (ac.) en MeOH para dar el compuesto del título (0,16 g, 51%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z = 457 $(M+H)^+$. ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,97- 7,94 (m, 2H), 7,71 (d, J = 7,8 Hz, 1H), 7,61 (s, 1H), 7,56-7,51 (m, 2H), 7,43 (dd, J = 7,6, 7,6 Hz, 1H), 4,67 (m, 1H), 4,22 (c, J = 7,1 Hz, 2H), 3,36-3,12 (m, 4H) y 1,38 (t, J = 7,1 Hz, 3H).

Ejemplo 93

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



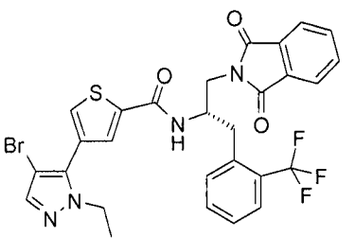
a) 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (0,45 g, 1,9 mmol) [véase el ejemplo 92(a)] en THF (5 ml) se le añadió NBS (0,33 g, 2,5 mmol). La mezcla de reacción se calentó a 78ºC en una atmósfera de nitrógeno. Después de 2 h, la mezcla de reacción se concentró al vacío y se

purificó sobre sílice (EtOAc/hexanos, 10-30%) para producir el compuesto del título (0,47 g, 78%). LC-MS (ES) m/z = 316 $(M+H)^+$.

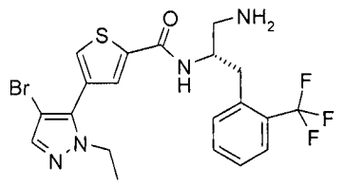
b) 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (0,2 g, 0,63 mmol) en THF/H_2O (5 ml/1 ml) se le añadió KOH (0,15 g, 2,4 mmol). La mezcla de reacción se calentó a 58°C durante 10 h y después se concentró y se diluyó con H_2O (2 ml). El valor del pH se ajustó a 6 con HCl acuoso. La mezcla se extrajo con DCM (3 x 5 ml) y las fracciones orgánicas recogidas se concentraron al vacío para dar el ácido 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxílico bruto, que se usó directamente sin purificación adicional. LC-MS (ES) m/z = 302 $(M+H)^+$.

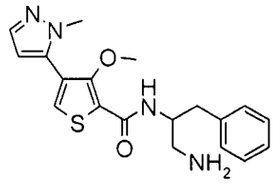
A una solución de ácido 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (156 mg, 0,52 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (0,18 g, 0,52 mmol) y DIPEA (0,5 ml, 2,86 mmol) en DCM (5 ml) a 25°C se le añadió en una porción PyBrOP (0,29 g, 0,62 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-60%/hexano), produciendo el compuesto del título (0,281 g, 86%). LC-MS (ES) m/z = 632 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



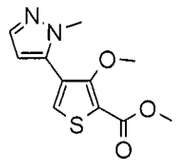
Se disolvió 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (250 mg, 0,39 mmol) en MeOH (5 ml) y la mezcla se trató con NH_2NH_2 (0,5 ml, 15,93 mmol). La mezcla se agitó a TA durante una noche y se concentró. El residuo se purificó por cromatografía en columna [sílice, MeOH al 2-10% en $CHCl_3$ (NH_4OH al 0,5%)], produciendo la base libre del compuesto del título, que se trató con HCl (ac.) en MeOH para dar el compuesto del título (144 mg, 51%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 502 $(M+H)^+$. ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,93-7,87 (m, 2H), 7,72 (d, J = 8,1 Hz, 1H), 7,62 (s, 1H), 7,57-7,51 (m, 2H), 7,43 (t, J = 6,6 Hz, 1H), 4,67 (m, 1H), 4,25 (c, J = 7,3 Hz, 2H), 3,37-3,11(m, 4H) y 1,37 (t, J = 7,1 Hz, 3H).

Ejemplo 94



Preparación de *N*-[2-amino-1-(fenilmetil)etil]-3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

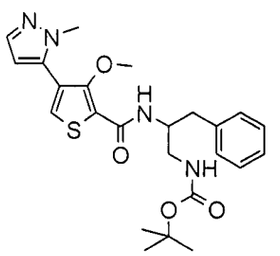
a) 3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Se combinaron 4-bromo-3-(metiloxi)-2-tiofenocarboxilato de metilo (250 mg, 0,10 mmol) [preparado de acuerdo con Corral, C.; El-Ashmawy, M.B.; Lissavetzky,

J.; Basilio, A.; Giraldez, A.; *Eur. J. Med. Chem. Chim. Ther.* 22; **1987**; 251-254], 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (250 mg, 1,20 mmol), $Pd(PPh_3)_4$ (58 mg, 49,8 μmol) y K_2CO_3 (550 mg, 3,98 mmol) en dioxano (5 ml) y H_2O (1 ml) en un tubo cerrado herméticamente. Después de 12 h a 80°C, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, MeOH al 0,5% en DCM), produciendo el compuesto del título (215 mg, 86%) en forma de un residuo pardo: LCMS (ES) m/z = 253 $(M+H)^+$.

b) [2-({[3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



i) Una solución de 3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (215 mg, 0,853 mmol) en NaOH 6 N (4 ml) y THF (4 ml) se agitó en un tubo cerrado herméticamente a 70°C. Después de 2 h, la solución se acidificó a un valor de pH de 3 usando HCl 1 N y después se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z = 239 $(M+H)^+$.

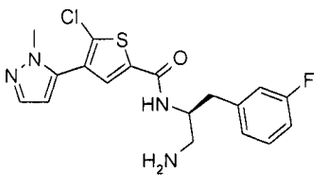
ii) A una solución del ácido bruto, (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (210 mg, 0,844 mmol) [de la Preparación 2] y diisopropiletil amina (735 μl, 4,22 mmol) en DCM (8 ml) se le añadió en una porción PyBrop (472 mg, 1,01 mmol). Después de 1 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente: LCMS (ES) m/z = 471 $(M+H)^+$.

c) N-[2-amino-1-(fenilmetil)etil]-3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

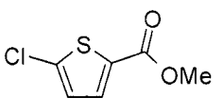
Una solución de [2-({[3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (en bruto, de la parte b) en TFA-DCM (3 ml, 1:2) se agitó a 25°C. Después de 30 min, la solución se concentró con un azeótropo de tolueno y el residuo se neutralizó a través de un lecho de sílice (MeOH al 3% en DCM (NH_4OH al 1%)), produciendo la base libre del compuesto del título.

Después, la base libre, en forma de una solución en MeOH, se trató con un exceso de HCl 4 M en dioxano, produciendo el compuesto del título (270 mg, 86%-2 etapas) en forma de la sal HCl: LCMS (ES) m/z 371 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,06 (s a, 3 H) 7,91 (s, 1 H) 7,72 (d, J = 8,59 Hz, 1 H) 7,52 (d, J = 1,77 Hz, 1 H) 7,25 - 7,31 (m, 4 H) 7,18 - 7,23 (m, 1 H) 6,39 (d, J = 2,02 Hz, 1 H) 4,52 (s a, 1 H) 3,78 (s, 3 H) 3,41 (s, 3 H) 2,97 - 3,05 (m, 4 H).

Ejemplo 95:



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

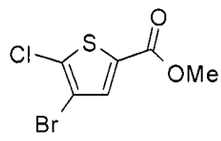


a) 5-cloro-2-tiofenocarboxilato de metilo

A una solución de ácido 5-cloro-2-tiofenocarboxílico (20 g, 123 mmol) en MeOH (200 ml) se le añadió H_2SO_4 conc. (5 ml). Después de calentar a 55°C durante 12 h, la solución de reacción se concentró y se diluyó con DCM (250 ml). La solución de DCM se lavó con $NaHCO_3$ acuoso y después con H_2O y se secó

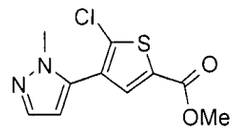
sobre Na_2SO_4. La concentración al vacío dio el compuesto del título en forma de un aceite de color amarillo (21,5 g, 99%): LCMS (ES) m/z 178 $(M+H)^+$.

b) 4-bromo-5-cloro-2-tiofenocarboxilato de metilo



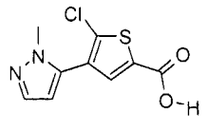
A un matraz de fondo redondo de 1 l se le añadieron cloruro de aluminio (11,32 g, 85 mmol) y 5-cloro-2-tiofenocarboxilato de metilo (10 g, 56,6 mmol) disuelto en $CHCl_3$ (250 ml). Se añadió gota a gota Br_2 (4,08 ml, 79 mmol) durante 10 minutos. Después de agitar durante 6 h a 25ºC, la solución de reacción de color naranja claro se lavó con $NaHCO_3$ sat. La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice [hexanos/EtOAc, 9:1] para dar el producto [12 g, 80%] en forma de un sólido de color blanco. LCMS (ES) m/z 256 $(M+H)^+$.

c) 5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



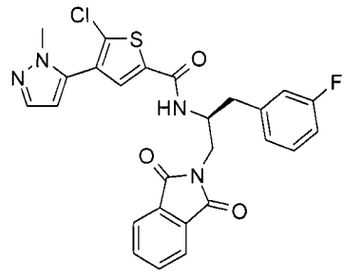
A un matraz cerrado herméticamente de 300 ml se le añadieron 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (8,14 g, 39,1 mmol), carbonato potásico (12,98 g, 94 mmol), 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (8 g, 31,3 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,40 g, 0,78 mmol) en 1,4-dioxano (50 ml) y H_2O (6 ml). Después de agitar durante 90 min a 75ºC, la solución de reacción se diluyó con DCM (100 ml) y se lavó con H_2O. La capa orgánica se secó Na_2SO_4, se filtró y se concentró. El residuo de reacción se purificó sobre gel de sílice [hexanos/EtOAc, 2:1] para dar el producto [5,7 g, 70%] en forma de un sólido de color castaño: LCMS (ES) m/z 258 $(M+H)^+$.

d) ácido 5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 250 ml se le añadieron 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (4,4 g, 17,14 mmol) e hidróxido sódico (28,6 ml, 171 mmol) en tetrahidrofurano (THF) (50 ml) y MeOH (50 ml). La solución de reacción se agitó a TA durante 12 h y después se hizo básica (pH ~2) con HCl 2,5 M y se extrajo con DCM. La capa orgánica se separó, se secó (Na_2SO_4) y se concentró para dar un sólido de color blanquecino (4,2 g, 94%) que se usó directamente sin purificación adicional: LCMS (ES) m/z 243 $(M+H)^+$.

e) 5-cloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



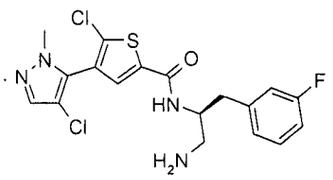
A un matraz de fondo redondo de 500 ml se le añadieron ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (4,2 g, 17,31 mmol), 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (6,37 g, 19,04 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6], N,N-diisopropil etilamina (4,53 ml, 26,0 mmol) y Pybrop (12,05 g, 26,0 mmol) en diclorometano (DCM) (150 ml). Después de agitar a TA durante 12 h, la solución de reacción se lavó con H_2O (2 x 100 ml) y la capa orgánica se secó Na_2SO_4, se filtró y se concentró. El producto bruto se añadió a una columna de gel de sílice y se eluyó con [EtOAc/hexanos, 1:1] para dar el producto [7,8 g, 86%] en forma de un sólido de color blanco: LCMS (ES) m/z 524 $(M+H)^+$.

f) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 250 ml se le añadieron 5-cloro-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (7,8 g, 14,91 mmol) e hidrazina (14,50 ml, 298 mmol) en tetrahidrofurano (THF) (75 ml) y metanol (75 ml). Después de 24 h a TA, el precipitado se filtró y el filtrado se concentró. El producto bruto se purificó sobre una columna de gel de sílice [$CHCl_3$/MeOH/NH_4OH, 90:9:1] para dar el compuesto del título en forma de un sólido de color blanco.

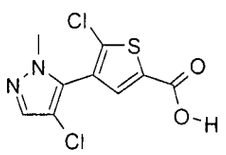
El producto de la base libre se trató con HCl 4 M en dioxano (15 ml). Después de 5 min, la solución se concentró y se secó al vacío para producir el producto (6,8 g, 95%) en forma de una sal HCl: LCMS (ES) m/z 467 $(M+H)^+$, ^1H RMN (400 MHz, CD3OD) ppm 7,97 (s, 2H), 7,31 (s, 1H), 7,14 (m, 2H), 6,98 (m, 1H), 6,75 (s, 1H), 4,54 (m, 1H), 3,98 (s, 3H), 3,24 (m, 2H), 3,04 (m, 2H).

Ejemplo 96



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

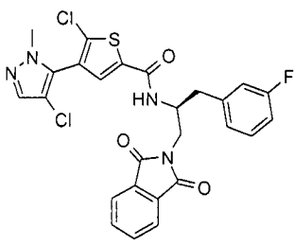
a) ácido 5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de 500 ml se le añadieron 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (5 g, 19,48 mmol) [del Ejemplo 95] y NCS (3,12 g, 23,37 mmol) en tetrahidrofurano (THF) (100 ml) (50 ml). Después de agitar durante 4 h a 70°C, la solución de reacción de color amarillo se trató con NaOH 6 M (32 ml, 195 mmol) y se agitó durante 2 horas más. La solución de reacción se diluyó con H_2O (50 ml) y DCM (200 ml). La capa orgánica se separó y la capa acuosa se hizo básica con HCl 6 N. La solución acuosa ácida se extrajo con DCM (3 x 200 ml), se

secó sobre Na_2SO_4 y se concentró para dar el producto bruto [2,6 g, 48%] en forma de un sólido de color castaño: LCMS (ES) m/z 277 $(M+H)^+$.

b) 5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 500 ml se le añadieron ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (6 g, 21,65 mmol), 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (7,25 g, 21,65 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6], N,N-diisopropil etilamina (5,67 ml, 32,5 mmol) y Pybrop (15,08 g, 32,5 mmol) en diclorometano (DCM) (150 ml). Después de agitar a TA durante 12 h, la solución de reacción se lavó con H_2O (2 x 100 ml) y la capa orgánica se secó Na_2SO_4, se filtró y se concentró. El producto bruto se añadió a una columna de gel de sílice y se eluyó con [EtOAc/hexanos, 1:1] para dar el producto [9,0 g, 74%] en forma de un sólido de color blanco: LCMS (ES) m/z 558 $(M+H)^+$.

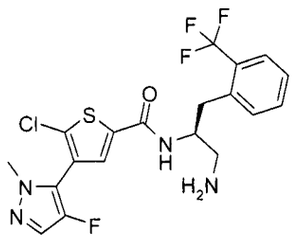
c) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 250 ml se le añadieron 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (9 g, 16,15 mmol) e hidrazina (15,69 ml, 323 mmol) en tetrahidrofurano (THF) (75 ml) y metanol (75 ml). Después de 24 h a TA, el precipitado se filtró, el filtrado se concentró y el producto bruto se purificó sobre una columna de gel de sílice [$CHCl_3$/MeOH/NH_4OH, 90:9:1] para dar el compuesto del título en forma de un sólido de color blanco.

El producto de la base libre se trató con HCl 4 M en dioxano (15 ml). Después de 5 min, la solución del producto se concentró y se secó al vacío para producir el

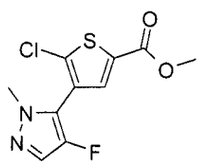
producto (6,5 g, 91%) en forma de una sal HCl: LCMS (ES) m/z 428 $(M+H)^+$, ^1H RMN (400 MHz, CD_3OD) ppm 7,75 (s, 1 H), 7,60 (s, 1H), 7,32 (m, 1H) 7,14 (m, 2H), 6,98 (m, 1H), 4,54 (m, 1H), 3,78 (s, 3H), 3,24 (m, 2H), 3,02 (m, 2H).

Ejemplo 97



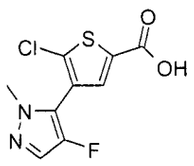
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



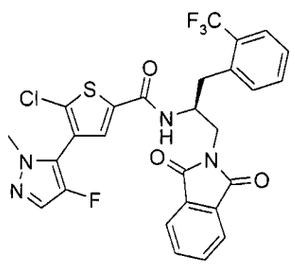
A una solución de 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (250 mg, 0,974 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 95] en acetonitrilo (4,864 ml) y H_2O (486 µl) se le añadió selectfluor (449 mg, 1,27 mmol). La solución resultante se agitó a 70°C en un tubo cerrado herméticamente durante 1 h, tiempo después del cual se añadió en una porción más cantidad de selectfluor (449 mg, 1,266 mmol). Después de agitar durante 12 h, la solución se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM-THF y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 10% en hexanos), produciendo 5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (65 mg, 0,237 mmol, rendimiento de 24,30%) en forma de un sólido de color amarillo; LCMS (ES) m/z 274, 276 (M, M+H).

b) ácido 5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



Una solución de 5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (65 mg, 0,237 mmol) en hidróxido sódico 6 N (0,39 ml, 2,37 mmol) y tetrahidrofurano (2 ml) se agitó a 70ºC en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (54 mg, 0,17 mmol, rendimiento de 72%) en forma de un aceite de color amarillo; LCMS (ES) m/e 261, 263 (M, M+2)+.

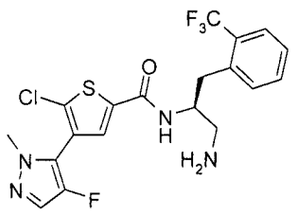
c) 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (53 mg, 0,203 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (78 mg, 0,203 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,18 ml, 1,02 mmol) en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (95 mg, 0,203 mmol). La solución se agitó a 25ºC durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 40%

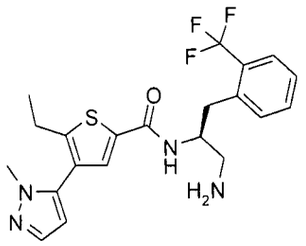
en hexanos), produciendo 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (106 mg, 0,129 mmol, rendimiento de 63,5%) en forma de un aceite transparente; LCMS (ES) m/e 591, 593 (M, M+H)+.

d) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



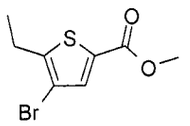
A una solución de 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (106 mg, 0,179 mmol) en tetrahidrofurano (1,095 ml) y metanol (1,095 ml) a 25°C se le añadió gota a gota hidrazina (0,056 ml, 1,79 mmol). Después de 48 h, la solución se concentró, se cargó en seco (sílice, MeOH al 5% en DCM (NH_4OH al 1%)) y se purificó inicialmente por cromatografía en columna. Después, el residuo se purificó adicionalmente por cromatografía de fase inversa Gilson usando una fase móvil al 2%-95%, produciendo la sal TFA del compuesto del título. Este compuesto se neutralizó a través de un lecho de sílice (MeOH al 5% en DCM (NH_4OH al 1%)), se concentró y se transfirió a la sal HCl añadiendo al residuo un exceso de HCl 4 M en dioxano (500 µl) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (17 mg, 0,029 mmol, rendimiento de 16,16%) en forma de un sólido de color blanco: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d6) ppm 9,11 (s,1 H) 8,11 (s, 1 H) 7,71 (s a, 3 H) 7,66 - 7,70 (m, 2H) 7,54 - 7,61 (m, 2H) 7,41 - 7,44 (m, 1 H) 4,47 (s a, 1 H) 3,79 (s, 3 H) 3,07 - 3,16 (m, 4 H).

Ejemplo 98



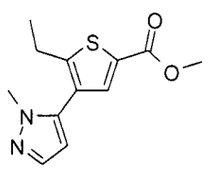
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 4-bromo-5-etil-2-tiofenocarboxilato de metilo



A una solución de ácido 4-bromo-5-etil-2-tiofenocarboxílico (1 g, 4,25 mmol) en metanol (21,27 ml) se le añadió ácido sulfúrico (0,23 ml, 4,25 mmol). La solución resultante se agitó a 50°C durante 48 h. Se añadió H_2O (50 ml) y la reacción se enfrió a 0°C en un baño de hielo. El valor del pH se ajustó a ~12 y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, proporcionando 4-bromo-5-etil-2-tiofenocarboxilato de metilo (1,060 g, 4,25 mmol, rendimiento de 100%): LCMS (ES) m/e 248, 250 (M, M+2)+.

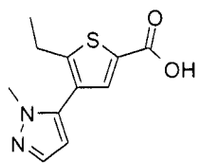
b) 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Se combinaron una solución de 4-bromo-5-etil-2-tiofenocarboxilato de metilo (300 mg, 1,204 mmol), carbonato potásico (832 mg, 6,02 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (326 mg, 1,565 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (30,8 mg, 0,060 mmol) en un tubo cerrado herméticamente y la mezcla se agitó a 80°C durante 1 h. Después, los contenidos de la reacción se repartieron entre H_2O y DCM y la fase

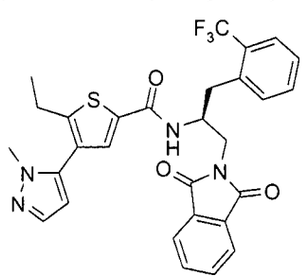
acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (301 mg, 1,204 mmol, rendimiento de 100%) en forma de un aceite pardo: LCMS (ES) m/e 251 $(M+H)^+$.

c) ácido 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



Una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (300 mg, 1,198 mmol) en hidróxido sódico 6 N (2,397 ml, 1,198 mmol) y tetrahidrofurano (5,992 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (283 mg, 1,2 mmol, rendimiento de 100%) en forma de un aceite de color amarillo; LCMS (ES) m/z = 236 $(M+H)^+$.

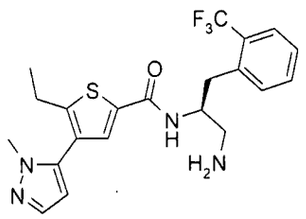
d) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (283 mg, 1,2 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (461 mg, 1,2 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (1,043 ml, 5,99 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (615 mg, 1,317 mmol).

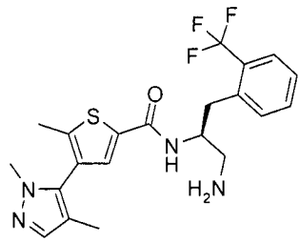
La solución se agitó a 25ºC durante 12 h y después se repartió entre H_2O y DCM: La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 50% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (486 mg, 0,86 mmol, rendimiento de 71,6%) en forma de un aceite transparente: LCMS (ES) m/e 567 (M+H)+.

e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



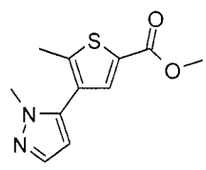
A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (486 mg, 0,86 mmol) en tetrahidrofurano (2,144 ml) y metanol (2,14 ml) a 25ºC se le añadió gota a gota hidrazina (0,269 ml, 8,58 mmol). Después de 12 h, la solución se concentró, se cargó en seco y se purificó por cromatografía en columna (sílice, MeOH al 5% en DCM (NH_4OH al 1%)). , Después, la base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (500 µl) en MeOH (2 ml), produciendo N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (250 mg, 0,491 mmol, rendimiento de 57,2%)-2 HCl en forma de un sólido de color blanco: LCMS (ES) m/z = 437 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d6) ppm 8,84 (d, J = 8,84 Hz, 1 H) 8,08 (s a, 3 H) 7,93 (s, 1 H) 7,69 (d, J = 7,83 Hz, 1 H) 7,51-7,61 (m, 3 H) 7,39 - 7,46 (m, 1 H) 6,34 (d, J = 2,02 Hz, 1 H) 4,48 (s a, 1 H) 3,77 (s, 3 H) 2,99-3,11 (m, 4 H) 2,74 (c, J = 7,49 Hz, 2 H) 1,16 (t, J = 7,45 Hz, 3 H).

Ejemplo 99



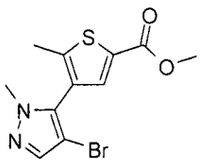
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



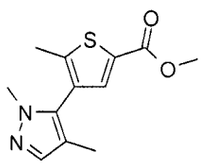
Una solución de 4-bromo-5-metil-2-tiofenocarboxilato de metilo (2 g, 8,51 mmol) [preparado en la Preparación 10], carbonato potásico (5,88 g, 42,5 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,124 g, 10,21 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (0,217 g, 0,425 mmol) en 1,4-dioxano (35,4 ml) y H_2O (7,09 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 1 h. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 25% en hexanos), produciendo 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo. Esta reacción se realizó en varias extracciones (1 g, 3 x 2 g) que se combinaron para el tratamiento y se purificaron, produciendo el compuesto del título (5,5 g, rendimiento combinado de 78%) en forma de un aceite viscoso de color amarillo: LCMS (ES) m/e 236 $(M+H)^+$.

b) 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo



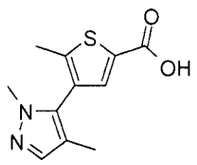
Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (580 mg, 2,45 mmol) y n-bromosuccinimida (437 mg, 2,45 mmol) en tetrahidrofurano (12,300 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Después, la solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y después se purificaron por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (600 mg, 1,90 mmol, rendimiento de 78%) en forma de un aceite de color amarillo: LCMS (ES) m/e 314, 316 (M, $M+H)^+$.

c) 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo



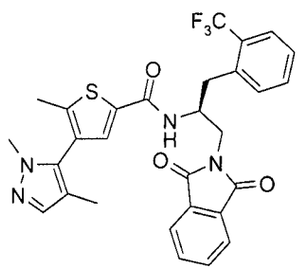
Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (420 mg, 1,33 mmol), carbonato potásico (921 mg, 6,66 mmol), $PdCl_2$(dppf) (98 mg, 0,13 mmol) y trimetilboroxina (0,371 ml, 2,67 mmol) en N,N-dimetilformamida (6,663 ml) se agitó a 110°C en un tubo cerrado herméticamente durante 2 h. Esta reacción se realizó en dos extracciones (100 mg and 420 mg) que se combinaron y se repartieron entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (240 mg, 58%) en forma de un aceite de color amarillo: LCMS (ES) m/e 251 $(M+H)^+$.

d) ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico



Una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (240 mg, 0,96 mmol) en hidróxido sódico 6 N (3,20 ml, 19,18 mmol) y tetrahidrofurano (4,79 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (217 mg, 0,92 mmol, rendimiento de 96%) en forma de un aceite de color amarillo: LCMS (ES) m/e 236 $(M+H)^+$.

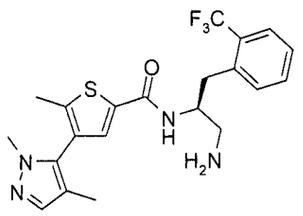
e) 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida



A una solución de 4-metil-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (217 mg, 0,918 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (353 mg, 0,92 mmol) [preparado de acuerdo con la Preparación 6] y diisopropiletilamina (0,800 ml, 4,59 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (472 mg, 1,01 mmol). La solución se agitó a 25°C durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida (373 mg, 0,66 mmol,

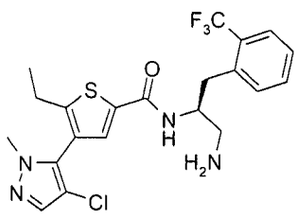
rendimiento de 71,7%) en forma de una espuma amarilla: LCMS (ES) m/e 567 (M+H)+.

f) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida



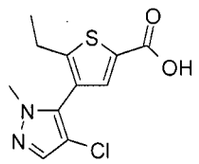
A una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida (373 mg, 0,66 mmol) en tetrahidrofurano (1,65 ml) y metanol (1,65 ml) a 25°C se le añadió gota a gota hidrazina (0,21 ml, 6,58 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (253 mg, 0,497 mmol, rendimiento de 75%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 437 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d6) ppm 8,80 (d, J = 8,59 Hz, 1 H) 8,09 (s a, 3 H) 7,82 (s, 1 H) 7,69 (d, J = 7,83 Hz, 1 H) 7,58 (t, J = 8,08 Hz, 1 H) 7,43 (t, J = 7,33 Hz, 1 H) 7,38 (s, 1 H) 4,47 (s a, 1 H) 3,64 (s, 3 H) 2,99 - 3,07 (m, 4 H) 2,27 (s, 3 H) 1,89 (s, 3 H).

Ejemplo 100



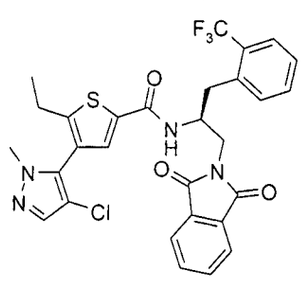
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida

a) ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico



Una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (300 mg, 1,2 mmol) [preparado en el Ejemplo 98] y N-clorosuccinimida (160 mg, 1,2 mmol) en tetrahidrofurano (6 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Se añadió en una porción hidróxido sódico 6 N (1 ml, 5,99 mmol) y la solución se agitó durante 1 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico (325 mg, 1,20 mmol, rendimiento de 100%) en forma de un aceite de color amarillo: LCMS (ES) m/e 271, 273 (M, M+2)$^+$.

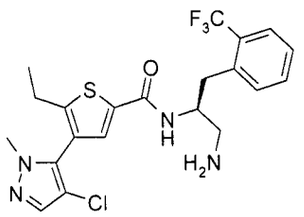
b) 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida



A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico (200 mg, 0,74 mmol), N,N-diisopropiletilamina (0,64 ml, 3,69 mmol) y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (284 mg, 0,74 mmol) [preparada de acuerdo con la Preparación 6] en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (414 mg, 0,886 mmol). La solución se agitó a 25°C durante 1 h y después se repartió

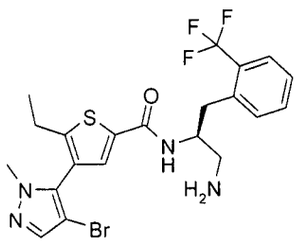
entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 50% en hexanos), produciendo 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida (316 mg, 0,526 mmol, rendimiento de 71%) en forma de una espuma de color blanco: LCMS (ES) m/e 601, 603 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida



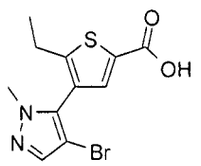
A una solución de 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida (316 mg, 0,53 mmol) en tetrahidrofurano (1,314 ml) y metanol (1,3 ml) a 25ºC se le añadió gota a gota hidrazina (0,16 ml, 5,26 mmol). Después de 12 h, la solución se concentró, se purificó por cromatografía en columna (sílice, MeOH al 5% en DCM (NH_4OH al 1%)) y se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 2 M en Et_2O (2 ml) en MeOH (5 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida (163 mg, 0,30 mmol, rendimiento de 57%) en forma de un sólido de color blanco: LCMS (ES) m/z = 471, 473 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d6) ppm 8,82 (s a, 1 H) 8,04 (s a, 3 H) 7,85 (s, 1 H) 7,65 - 7,72 (m, 2 H) 7,52-7,59 (m, 2 H) 7,39 - 7,46 (m, 1 H) 4,41-4,47 (m, 1 H) 3,71 (s, 3 H) 2,98-3,07 (m, 4H) 2,67 (c, J = 7,58 Hz, 2 H) 1,16 (t, J = 7,58 Hz, 3 H).

Ejemplo 101



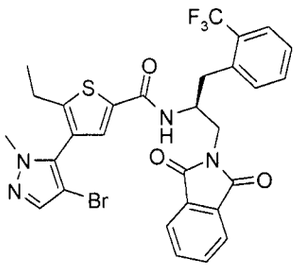
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida

a) ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico



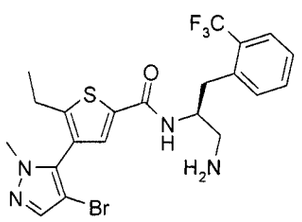
Una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (300 mg, 1,2 mmol) [preparado en el Ejemplo 98] y N-bromosuccinimida (213 mg, 1,2 mmol) en tetrahidrofurano (5,99 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Se añadió en una porción hidróxido sódico acuoso (4,0 ml, 23,97 mmol) y la solución se agitó durante 1 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y después se purificaron por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico (378 mg, 1,2 mmol, rendimiento de 100%) en forma de un aceite de color amarillo: LCMS (ES) m/e 314, 316 $(M, M+2)^+$.

b) 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida



A una solución de ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico (200 mg, 0,57 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (181 mg, 0,57 mmol) [preparada de acuerdo con la Preparación 6] y N,N-diisopropiletilamina (0,50 ml, 2,87 mmol) en diclorometano (4,23 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (295 mg, 0,632 mmol). La solución se agitó a 25ºC durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 50% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida (240 mg, 0,37 mmol, rendimiento de 64,8%) en forma de una espuma de color blanco: LCMS (ES) m/e 645, 647 $(M, M+2)^+$.

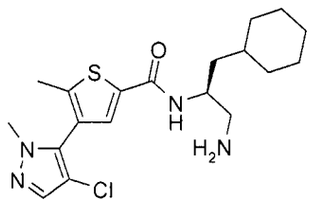
c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida



A una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida (240 mg, 0,37 mmol) en tetrahidrofurano (1,31 ml) y metanol (1,31 ml) a 25ºC se le añadió gota a gota hidrazina (0,12 ml, 3,72 mmol). Después de 12 h, la solución se concentró, se purificó por cromatografía en columna (sílice, MeOH al 5% en DCM (NH_4OH al 1%)) y se convirtió en la sal HCl mediante la

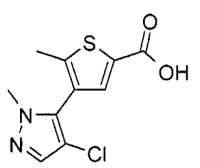
adición al residuo de un exceso de HCl 4 M en dioxano (2 ml) en MeOH (5 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida (167 mg, 0,28 mmol, rendimiento de 76%) en forma de un sólido de color blanco: LCMS (ES) m/z = 515, 517 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d6) ppm 8,77 (dd, J = 15,66, 9,09 Hz, 1 H) 8,02 (s a, 3 H) 7,80 (s, 1 H) 7,66 - 7,72 (m, 2 H) 7,54 - 7,61 (m, 2 H) 7,41 - 7,48 (m, 1 H) 4,42 - 4,47 (m, 1 H) 3,71 (s, 3 H) 2,98 - 3,06 (m, 4 H) 2,66 (dd, J = 7,45, 3,16 Hz, 2 H) 1,15 (t, J = 7,45 Hz, 3 H).

Ejemplo 102



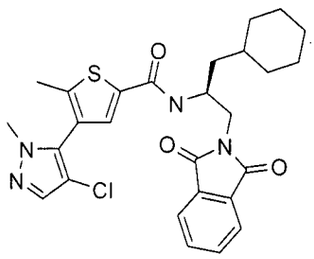
Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico



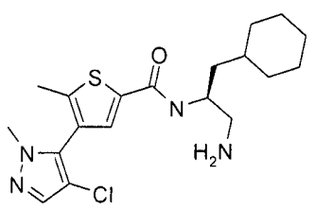
Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,75 g, 11,64 mmol) [preparado en el Ejemplo 99] y N-clorosuccinimida (1,55 g, 11,64 mmol) en tetrahidrofurano (58 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70ºC. Se añadió en una porción hidróxido sódico (9,70 ml, 58 mmol) y la solución se agitó durante 1 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y después se purificaron por cromatografía en columna (sílice, EtOAc al 20% en hexanos), produciendo ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (2,3 g, 8,96 mmol, rendimiento de 77%) en forma de un aceite de color amarillo: LCMS (ES) m/e 257, 259 (M, M+2)+.

b) 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida



A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (159 mg, 0,62 mmol), N,N-diisopropiletilamina (0,54 ml, 3,10 mmol) y 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,62 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3-ciclohexil-N-{[(1,1-dimetiletil)oxi]carbonil}-L-alanina (5 g, 18,4 mmol)] en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (347 mg, 0,74 mmol). La solución se agitó a 25°C durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 45% en hexanos), produciendo 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida (231 mg, 0,44 mmol, rendimiento de 71%) en forma de un aceite transparente: LCMS (ES) m/e 525, 527 (M, M+2)$^+$.

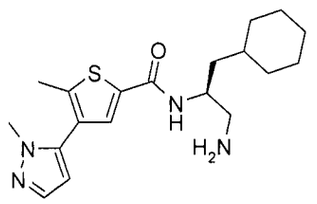
c) N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida



A una solución de 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida (231

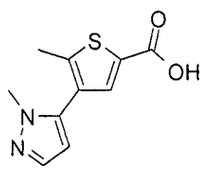
mg, 0,44 mmol) en tetrahidrofurano (2,20 ml) y metanol (2,20 ml) a 25°C se le añadió gota a gota hidrazina (0,14 ml, 4,40 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). Después, la base libre se transfirió a la sal HCl añadiendo al residuo un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (124 mg, 0,27 mmol, rendimiento de 60%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 394, 396 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,51 (s a, 1 H) 7,97 (s a, 3 H) 7,86 (s, 1 H) 7,70 (s, 1 H) 4,24 - 4,26 (m, 1 H) 3,71 (s, 3 H) 2,90 - 2,99 (m, 2 H) 2,36 (s, 3 H) 1,75 - 1,79 (m, 1 H) 1,61 1,64 (m, 4 H) 1,48 - 1,51 (m, 1 H) 1,31 - 1,36 (m, 2 H) 1,10 - 1,14 (m, 2 H) 0,91 - 0,94 (m, 2 H).

Ejemplo 103



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

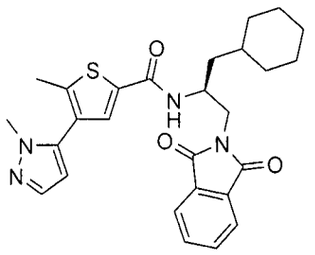
a) ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (250 mg, 1,06 mmol) [preparado en el Ejemplo 99] en hidróxido sódico 6 N (1,76 ml, 10,6 mmol) y tetrahidrofurano (5,290 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se

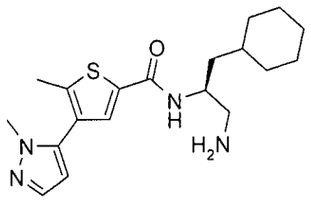
lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (151 mg, 0,68 mmol, rendimiento de 64%) en forma de un sólido de color blanco; LCMS (ES) m/z = 223 $(M+H)^+$.

b) N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



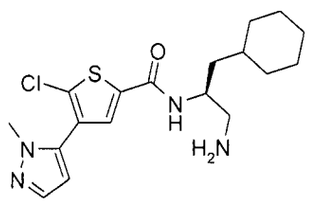
A una solución de ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (138 mg, 0,62 mmol), N,N-diisopropiletilamina (0,541 ml, 3,10 mmol) y 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,62 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3-ciclohexil-N-{[(1,1-dimetiletil)oxi]carbonil}-L-alanina (5 g, 18,4 mmol)] en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (347 mg, 0,74 mmol). La solución se agitó a 25°C durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 50% en hexanos), produciendo N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (285 mg, 0,581 mmol, rendimiento de 94%) en forma de una espuma de color blanco: LCMS (ES) m/e 491, 493 (M, M+2)$^+$.

c) N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



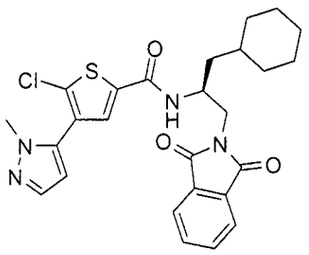
A una solución de N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (285 mg, 0,581 mmol) en tetrahidrofurano (2,905 ml) y metanol (2,91 ml) a 25ºC se le añadió gota a gota hidrazina (0,18 ml, 5,81 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). Después, la base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (173 mg, 0,40 mmol, rendimiento de 69%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 360 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,55 (d, J = 8,59 Hz, 1 H) 8,01 (s a, 3) 7,94 (s, 1 H) 7,52 (d, J = 2,02 Hz, 1 H) 6,35 (d, J = 1,77 Hz, 1 H) 4,24 - 4,27 (m, 1 H) 3,77 (s, 3 H) 2,91 - 2,94 (m, 2 H) 2,39 (s, 3 H) 1,72 - 1,77 (m, 1 H) 1,60 - 1,64 (m, 4 H) 1,49 - 1,52 (m, 1 H) 1,21 - 1,29 (m, 2 H) 1,15 - 1,25 (m, 2 H) 0,89 - 0,94 (m, 2 H).

Ejemplo 104



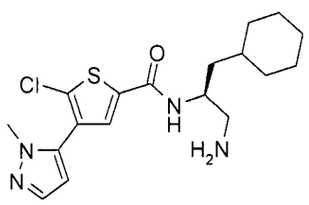
Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (150 mg, 0,62 mmol) [preparado en el Ejemplo 95], N,N-diisopropiletilamina (0,54 ml, 3,10 mmol) y 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,62 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3-ciclohexil-N-{[(1,1-dimetiletil)oxi]carbonil}-L-alanina (5 g, 18,4 mmol)] en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (347 mg, 0,74 mmol). La solución se agitó a 25°C durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 45% en hexanos), produciendo 5-cloro-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (168 mg, 0,33 mmol, rendimiento de 53%) en forma de un aceite transparente: LCMS (ES) m/e 511, 513 (M, M+2)$^+$.

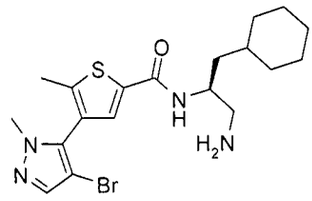
b) N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de 5-cloro-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (168 mg, 0,33 mmol) en tetrahidrofurano (1,644 ml) y metanol (1,644 ml) a 25°C se le añadió gota a gota hidrazina (0,10 ml, 3,29 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice,

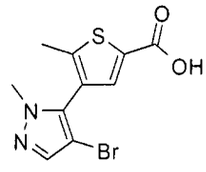
MeOH al 5% en DCM (NH_4OH al 1%)). Después, la base libre se transfirió a la sal HCl añadiendo al residuo un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (79 mg, 0,17 mmol, rendimiento de 53%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 380, 382 $(M, M+2)^+$, ^1H RMN (400 MHz, DMSO-d_6) δ ppm 8,82 (d, *J* = 8,59 Hz, 1 H) 8,10 (s, 1 H) 7,99 (s a, 3 H) 7,55 (d, *J* = 1,77 Hz, 1 H) 6,48 (d, *J* = 2,02 Hz, 1 H) 4,22 - 4,28 (m, 1 H) 3,81 (s, 3 H) 2,90 - 2,95 (m, 2 H) 1,74 - 1,78 (m, 1 H) 1,62 - 1,65 (m, 4 H) 1,48-1,51 (m, 1 H) 1,37 - 1,39 (m, 2 H) 1,09 - 1,13 (m, 2 H) 0,92 - 0,96 (m, 2 H).

Ejemplo 105



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

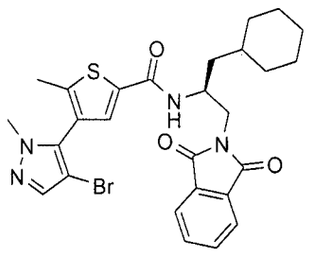
a) ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico



Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (250 mg, 1,058 mmol) [preparado en el Ejemplo 99] y N-bromosuccinimida (188 mg, 1,06 mmol) en tetrahidrofurano (5,29 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Se añadió en una porción hidróxido sódico (3,53 ml, 21,16 mmol) y la solución se agitó durante 1 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(4-bromo-1-metil-

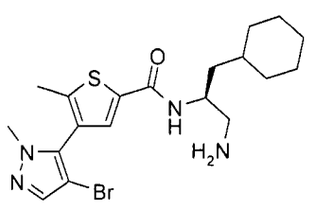
1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (289 mg, 0,96 mmol, rendimiento de 91%) en forma de un aceite de color amarillo: LCMS (ES) m/e 301, 303 (M, M+2)$^+$.

b) 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida



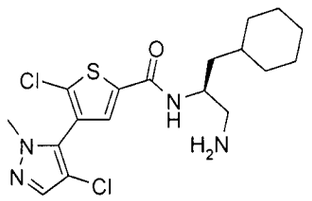
A una solución de ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (187 mg, 0,62 mmol), N,N-diisopropiletilamina (0,54 ml, 3,10 mmol) y 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,62 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3-ciclohexil-N-{[(1,1-dimetiletil)oxi]carbonil}-L-alanina (5 g, 18,4 mmol)] en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (347 mg, 0,74 mmol). La solución se agitó a 25ºC durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 50% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida (226 mg, 0,40 mmol, rendimiento de 64%) en forma de una espuma de color blanco: LCMS (ES) m/e 569, 571 (M, M+2)$^+$.

c) N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida



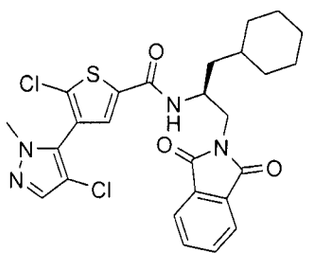
A una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida (226 mg, 0,40 mmol) en tetrahidrofurano (1,98 ml) y metanol (1,98 ml) a 25°C se le añadió gota a gota hidrazina (0,13 ml, 3,97 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna. Después, la base libre se transfirió a la sal HCl añadiendo al residuo un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (153 mg, 0,30 mmol, rendimiento de 75%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 439, 441 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,51 (s a, 1 H) 7,96 (s a, 3 H) 7,83 (s a, 1 H) 7,70 (s, 1 H) 4,21 - 4,25 (m, 1 H) 3,94 (s, 3H) 2,89 - 2,92 (m, 2 H) 2,35 (s, 3 H) 1,76 - 1,79 (m, 1 H) 1,60 - 1,64 (m, 4 H) 1,48 - 1,54 (m, 1 H) 1,26 - 1,32 (m, 2 H) 1,09 - 1,16 (m, 2 H) 0,92 - 0,95 (m, 1 H) 0,82 - 0,86 (m, 1 H).

Ejemplo 106



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

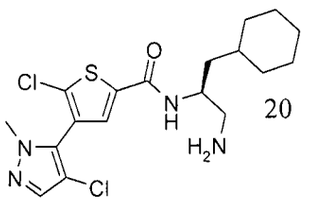
a) 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida



A una solución de ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (216 mg, 0,78 mmol) [preparado de acuerdo con el Ejemplo 96],

N,N-diisopropiletilamina (0,68 ml, 3,90 mmol) y 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (252 mg, 0,78 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3-ciclohexil-N-{[(1,1-dimetiletil)oxi]carbonil}-L-alanina (5 g, 18,4 mmol)] en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (401 mg, 0,86 mmol). La solución se agitó a 25°C durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 40% en hexanos), produciendo 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (303 mg, 0,55 mmol, rendimiento de 71%) en forma de un aceite transparente: LCMS (ES) m/e 545, 547 (M, M+2)$^+$.

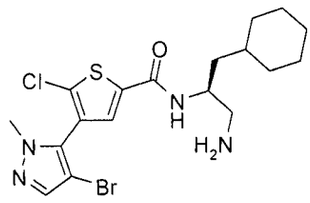
b) N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (303 mg, 0,55 mmol) en tetrahidrofurano (2,78 ml) y metanol (2,78 ml) a 25°C se le añadió gota a gota hidrazina (0,17 ml, 5,55 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). Después, la base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (190 mg, 0,389 mmol, rendimiento de 70,0%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 415, 417 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,84 (s a, 1 H) 8,06 (s, 4 H) 7,74 (s, 1 H) 4,25 (dd, J = 8,84, 4,29 Hz, 1 H) 3,77 (s, 3 H) 2,87 - 2,93 (m, 2 H) 1,71

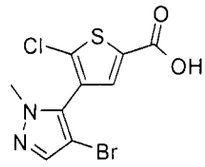
- 1,79 (m, 1H) 1,64 (d, *J* = 9,85 Hz, 3 H) 1,54 (s a, 1 H) 1,48 (s a, 1 H) 1,37 (dd, *J* = 13,26, 4,93 Hz, 1 H) 1,14 (s a, 1 H) 1,17 (d, *J* = 7,33 Hz, 2 H) 0,93 (d, *J* = 10,86 Hz, 1 H) 0,82 - 0,89 (m, 1 H).

Ejemplo 107



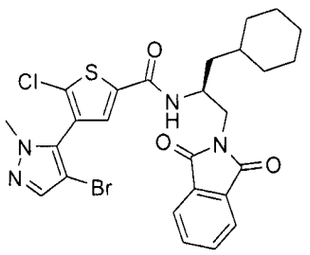
Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

a) ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxílico



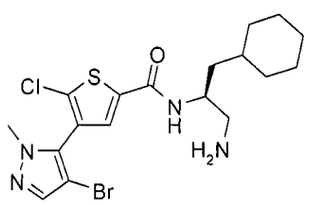
Una solución de ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (50 mg, 0,21 mmol) [preparado en el Ejemplo 95] y NBS (36,7 mg, 0,21 mmol) en tetrahidrofurano (2,06 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxílico (82 mg, 0,16 mmol, rendimiento de 79%) en forma de un aceite de color amarillo: LCMS (ES) m/e 257, 259 $(M, M+2)^+$.

b) 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida



A una solución de ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxílico (81 mg, 0,252 mmol), N,N-diisopropiletilamina (0,22 ml, 1,26 mmol) y 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (81 mg, 0,25 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (141 mg, 0,302 mmol). La solución se agitó a 25°C durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 40% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (47 mg, 0,080 mmol, rendimiento de 31,6%) en forma de un aceite transparente: LCMS (ES) m/e 589, 591 (M, M+2)$^+$.

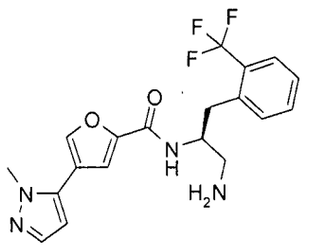
c) N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida



A una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (48 mg, 0,08 mmol) en tetrahidrofurano (0,41 ml) y metanol (0,41 ml) a 25°C se le añadió gota a gota hidrazina (0,03 ml, 0,81 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). Después, la base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-

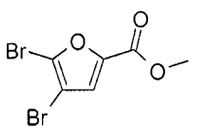
bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida (11 mg, 0,02 mmol, rendimiento de 24%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 459, 461 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,73 (s a, 1 H) 7,96 (s a, 4 H) 7,74 (s, 1 H) 4,21 - 4,26 (m, 1 H) 3,77 (s, 3 H) 2,92 - 2,99 (m, 2 H) 1,73 - 1,79 (m, 1 H) 1,62 - 1,67 (m, 4 H) 1,49 - 1,51 (m, 1 H) 1,25 (s a, 2 H) 1,06 - 1,13 (m, 2 H) 0,95 (d, J = 6,82 Hz, 1 H) 0,82 - 0,89 (m, 1 H).

Ejemplo 108



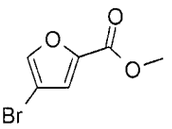
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

a) 4,5-dibromo-2-furanocarboxilato de metilo



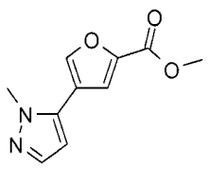
A una solución de ácido 4,5-dibromo-2-furanocarboxílico (5,7 g, 21,1 mmol) en metanol (106 ml) se le añadió ácido sulfúrico (11,3 ml, 211 mmol). La solución resultante se agitó a 50°C durante 4 días. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, proporcionando 4,5-dibromo-2-furanocarboxilato de metilo (5,5 g, 19,4 mmol, rendimiento de 92%): LCMS (ES) m/e 283 (M+H)$^+$.

b) 4-bromo-2-furanocarboxilato de metilo



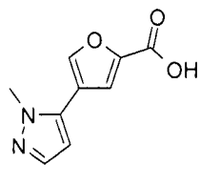
A una solución de 4,5-dibromo-2-furanocarboxilato de metilo (1 g, 3,52 mmol) en tetrahidrofurano (14,1 ml) a -40°C se le añadió cloruro de isopropilmagnesio (1,85 ml, 3,70 mmol). Después de 2 h, se añadió H_2O (3,52 ml) y la solución se calentó a 25°C. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 3% en hexanos), produciendo, 4-bromo-2-furanocarboxilato de metilo (470 mg, 2,04 mmol, rendimiento de 58%) en forma de un sólido de color blanco: LCMS (ES) m/e 204, 206 (M, M+2)$^+$.

c) 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo



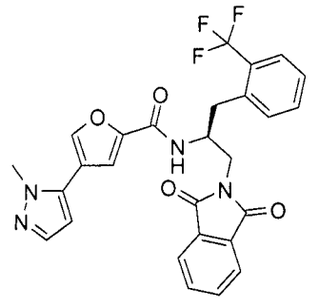
Una solución de 4-bromo-2-furanocarboxilato de metilo (470 mg, 2,29 mmol), carbonato potásico (1,58 g, 11,46 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (525 mg, 2,52 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (58,6 mg, 0,115 mmol) en 1,4-dioxano (9,5 ml) y agua (1,9 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 1 h. La solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 30% en hexanos), produciendo 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (124 mg, 0,60 mmol, rendimiento de 26%) en forma de un polvo de color blanco: LCMS (ES) m/e 206 (M+H)$^+$.

d) ácido 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico



Una solución de 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (124 mg, 0,60 mmol) en hidróxido sódico 6 N (2,0 ml, 12,0 mmol) y tetrahidrofurano (3,0 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 2 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico (54 mg, 0,28 mmol, rendimiento de 47%) en forma de un sólido de color blanco: LCMS (ES) m/e 192 $(M+H)^+$.

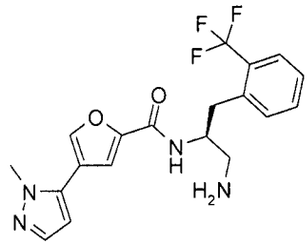
e) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida



A una solución de ácido 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico (54 mg, 0,28 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (108 mg, 0,28 mmol) [preparada en la Preparación 6] y N,N-diisopropiletilamina (0,24 ml, 1,40 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (158 mg, 0,34 mmol). La solución se agitó a 25°C durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 50% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-

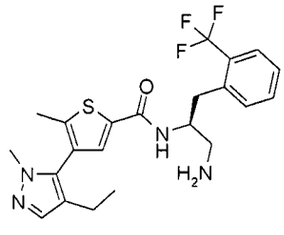
2-furanocarboxamida (100 mg, 0,14 mmol, rendimiento de 50%) en forma de un sólido de color blanco: LCMS (ES) m/e 523 $(M+H)^+$.

f) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida



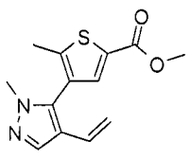
A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (100 mg, 0,19 mmol) en tetrahidrofurano (1 ml) y metanol (1 ml) a 25°C se le añadió gota a gota hidrazina (0,06 ml, 1,91 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (56 mg, 0,12 mmol, rendimiento de 62%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 393 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,70 (d, J = 9,09 Hz, 1 H) 8,28 (s, 1 H) 8,07 (s a, 3 H) 7,69 (d, J = 8,08 Hz, 1 H) 7,56 (d, J = 8,08 Hz, 2 H) 7,50 (s, 1 H) 7,45 (d, J = 1,77 Hz, 2 H) 6,51 (d, J = 1,77 Hz, 1 H) 4,50 - 4,57 (m, 1 H) 3,93 (s, 3 H) 3,02 - 3,16 (m, 4 H).

Ejemplo 109



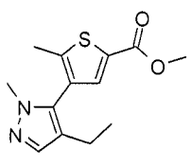
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo



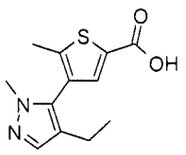
Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (200 mg, 0,64 mmol) [preparado en el Ejemplo 99], carbonato potásico (438 mg, 3,17 mmol), bis(tri-t-butilfosfina)paladio (0) (324 mg, 0,64 mmol) y complejo de 2,4,6-trivinilcicloboroxano-piridina (77 mg, 0,32 mmol) en 1,4-dioxano (5,3 ml) y H_2O (1 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 12 h. Los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (135 mg, 0,515 mmol, rendimiento de 81%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 250 $(M+H)^+$.

b) 4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo



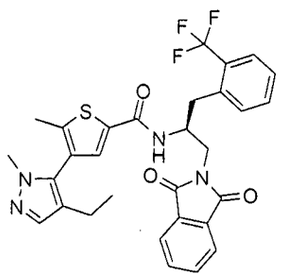
A una solución de 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (135 mg, 0,52 mmol) en metanol (2,6 ml) se le añadió Pd-C (21,9 mg, 0,21 mmol). La mezcla de reacción se hidrogenó a 1 atm (globo) durante 1 h. Después, la solución se purgó con N_2, se filtró a través de Celite y se concentró, produciendo 4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (145 mg, 0,51 mmol, rendimiento de 99%) en forma de un aceite de color amarillo que se usó sin purificación adicional: LCMS (ES) m/e 265 $(M+H)^+$.

c) ácido 4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico



Una solución de 4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (145 mg, 0,55 mmol) en hidróxido sódico 6 N (1,8 ml, 10,97 mmol) y tetrahidrofurano (4,8 ml) se agitó a 60°C en un tubo cerrado herméticamente durante 12 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (137 mg, 0,55 mmol, rendimiento de 100%) en forma de un aceite de color amarillo: LCMS (ES) m/e 250 $(M+H)^+$.

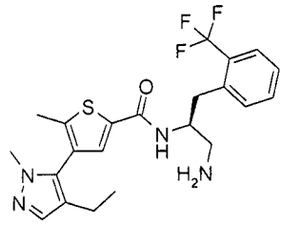
d) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida



A una solución de ácido 4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (137 mg, 0,55 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (211 mg, 0,55 mmol) [preparada en la Preparación 6] y diisopropiletilamina (0,48 ml, 2,74 mmol) en diclorometano (5,47 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (281 mg, 0,60 mmol). La solución se agitó a 25°C durante 1 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 40-70% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-

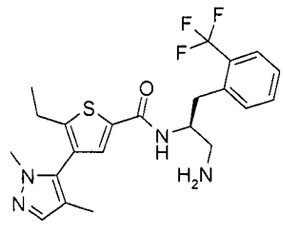
{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (262 mg, 0,45 mmol, rendimiento de 82%) en forma de un aceite transparente: LCMS (ES) m/e 581 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida



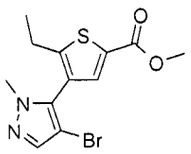
A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (262 mg, 0,45 mmol) en tetrahidrofurano (2,256 ml) y metanol (2,256 ml) a 25°C se le añadió gota a gota hidrazina (0,14 ml, 4,51 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (170 mg, 0,32 mmol, rendimiento de 72%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 451 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,72 (s a, 1 H) 8,05 (s a, 2 H) 7,76 (s, 1 H) 7,69 (d, J = 7,83 Hz, 1 H) 7,49 - 7,52 (m, 2 H) 7,40 - 7,45 (m, 2 H) 4,42 - 4,47 (m, 1 H) 3,61 (s a, 3 H) 3,01 - 3,07 (m, 4 H) 2,52 - 2,59 (m, 2 H) 2,26 (s, 3 H) 1,02 - 1,09 (m, 3 H).

Ejemplo 110



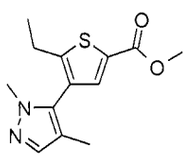
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo



Una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (980 mg, 3,92 mmol) [preparado en el Ejemplo 98] y N-bromosuccinimida (697 mg, 3,92 mmol) en tetrahidrofurano (19,6 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70ºC. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y después se purificaron por cromatografía en columna (sílice, EtOAc al 10-40% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (1,1 g, 3,34 mmol, rendimiento de 85%) en forma de un aceite de color amarillo: LCMS (ES) m/e 329, 331 $(M, M+2)^+$.

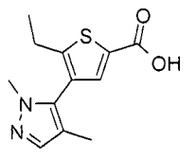
b) 4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo



Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (300 mg, 0,911 mmol), carbonato potásico (630 mg, 4,56 mmol), $PdCl_2$(dppf) (66,7 mg, 0,091 mmol) y trimetilboroxina (0,25 ml, 1,82 mmol) en N,N-dimetilformamida (9,1 ml) se agitó a 110ºC en un tubo cerrado herméticamente durante 2 h. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (143 mg, 0,51 mmol,

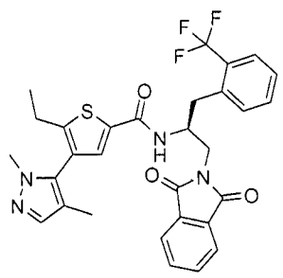
rendimiento de 56%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 265 $(M+H)^+$.

c) ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico



Una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (143 mg, 0,54 mmol) en hidróxido sódico 6 N (0,90 ml, 5,41 mmol) y tetrahidrofurano (5,4 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico (136 mg, 0,54 mmol, rendimiento de 100%) en forma de un aceite de color amarillo: LCMS (ES) m/e 251 $(M+H)^+$.

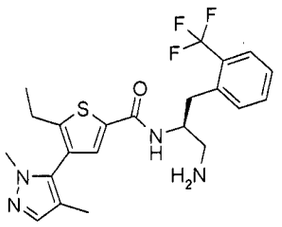
d) 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida



A una solución de ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxílico (130 mg, 0,52 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (200 mg, 0,52 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,45 ml, 2,60 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (267 mg, 0,57 mmol). La solución se agitó a 25°C durante 12 h,

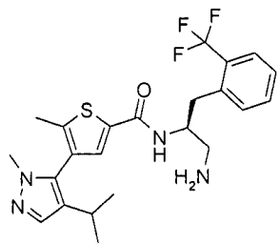
después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida (278 mg, 0,43 mmol, rendimiento de 82%) en forma de un aceite de color amarillo: LCMS (ES) m/e 581 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida



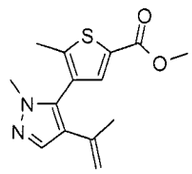
A una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-tiofenocarboxamida (278 mg, 0,48 mmol) en tetrahidrofurano (2,4 ml) y metanol (2,4 ml) a 25ºC se le añadió gota a gota hidrazina (0,15 ml, 4,79 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 3-15% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 2 M en Et_2O (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida (196 mg, 0,36 mmol, rendimiento de 76%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 451 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,86 - 8,93 (m, 1 H) 8,15 (s a, 3 H) 7,83 (s, 1 H) 7,69 (d, J = 7,58 Hz, 1 H) 7,55 (s a, 1 H) 7,52 (t, J = 7,45 Hz, 1 H) 7,42 (t, J = 7,45 Hz, 1 H) 7,38 (s, 1 H) 4,22 - 4,27 (m,1 H) 3,62 (s, 3 H) 2,97 - 3,09 (m, 4 H) 2,60 (c, J = 7,49 Hz, 2 H) 1,88 (s, 3 H) 1,13 (t, J = 7,58 Hz, 3 H).

Ejemplo 111



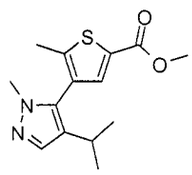
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida

a) 5-metil-4-[1-metil-4-(1-metiletenil)-1H-pirazol-5-il]-2-tiofenocarboxilato de metilo



Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (300 mg, 0,95 mmol), carbonato potásico (658 mg, 4,76 mmol), bis(tri-t-butilfosfina)paladio (0) (24,32 mg, 0,05 mmol) y 4,4,5,5-tetrametil-2-(1-metiletenil)-1,3,2-dioxaborolano (0,18 ml, 0,95 mmol) en 1,4-dioxano (5,3 ml) y H_2O (1,0 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 12 h. Los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 5-metil-4-[1-metil-4-(1-metiletenil)-1H-pirazol-5-il]-2-tiofenocarboxilato de metilo (171 mg, 0,58 mmol, rendimiento de 61%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 276 $(M+H)^+$.

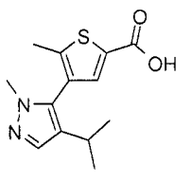
b) 5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxilato de metilo



A una solución de 5-metil-4-[1-metil-4-(1-metiletenil)-1H-pirazol-5-il]-2-tiofenocarboxilato de metilo (171 mg, 0,62 mmol) en metanol (3 ml) se le añadió $PdOH_2$ (34,8 mg, 0,25 mmol). La mezcla de reacción se hidrogenó a 1 atm (globo)

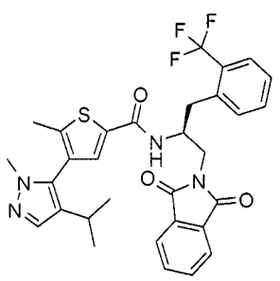
durante 1 h. Después, la solución se purgó con N_2, se filtró a través de Celite y se concentró, produciendo 5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxilato de metilo (173 mg, 0,62 mmol, rendimiento de 100%) en forma de un aceite transparente que se usó sin purificación adicional: LCMS (ES) m/e 279 $(M+H)^+$.

c) ácido 5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxílico



Una solución de 5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxilato de metilo (173 mg, 0,62 mmol) en hidróxido sódico 6 N (1 ml, 6,21 mmol) y tetrahidrofurano (5,4 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxílico (148 mg, 0,49 mmol, rendimiento de 79%) en forma de una espuma de color blanco: LCMS (ES) m/e 265 $(M+H)^+$.

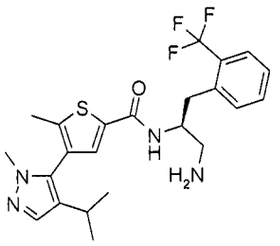
d) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida



A una solución de ácido 5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxílico (137 mg, 0,52 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (200 mg, 0,52 mmol)

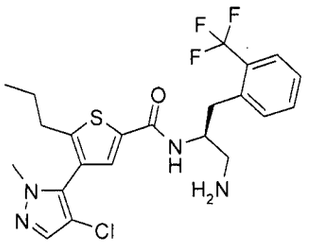
[preparada en la Preparación 6] y diisopropiletilamina (0,45 ml, 2,60 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (267 mg, 0,572 mmol). La solución se agitó a 25°C durante 12 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida (211 mg, 0,334 mmol, rendimiento de 64,2%) en forma de un aceite de color amarillo: LCMS (ES) m/e 595 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida



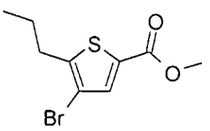
A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida (211 mg, 0,36 mmol) en tetrahidrofurano (2,4 ml) y metanol (2,4 ml) a 25°C se le añadió gota a gota hidrazina (0,11 ml, 3,55 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida (108 mg, 0,20 mmol, rendimiento de 57%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 465 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,71 (d, J = 8,59 Hz, 1 H) 8,07 (s a, 3 H) 7,74 (s, 1 H) 7,65 - 7,68 (m, 1 H) 7,55 - 7,60 (m, 1 H) 7,46 - 7,49 (m, 1 H) 7,39 - 7,46 (m, 2 H) 4,47 (s a, 1 H) 3,57 (s, 3 H) 2,99 - 3,05 (m, 4 H) 2,49 - 2,52 (m, 1 H) 2,25 (s, 3 H) 1,07 - 1,14 (m, 6 H).

Ejemplo 112



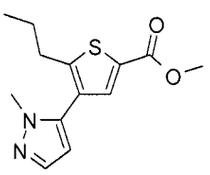
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida

a) 4-bromo-5-propil-2-tiofenocarboxilato de metilo



A una solución de ácido 4-bromo-5-propil-2-tiofenocarboxílico (5,0 g, 20,07 mmol) en metanol (100 ml) se le añadió ácido sulfúrico (5,35 ml, 100 mmol). La solución resultante se agitó a 50°C durante 36 h. Se añadió H_2O (50 ml) y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se lavaron con $NaHCO_3$ saturado, se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, proporcionando 4-bromo-5-propil-2-tiofenocarboxilato de metilo (5,1 g, 18,61 mmol, rendimiento de 93%) en forma de un aceite de color amarillo: LCMS (ES) m/e 262, 264 (M, M+2)$^+$.

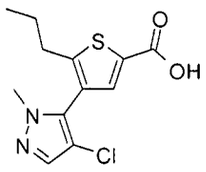
b) 4-(1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo



Una solución de 4-bromo-5-propil-2-tiofenocarboxilato de metilo (1,0 g, 3,80 mmol), carbonato potásico (2,63 g, 19,00 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (0,949 g, 4,56 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (0,097 g, 0,19 mmol) se combinaron en un tubo cerrado herméticamente y la mezcla se agitó a 80°C durante 1 h.

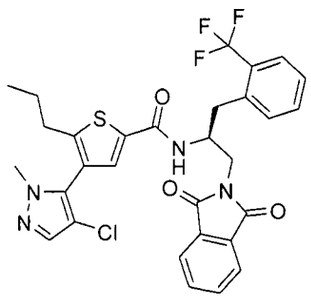
Después, los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (1,07 g, 3,76 mmol, rendimiento de 99%) en forma de un aceite de color amarillo: LCMS (ES) m/e 265 $(M+H)^+$.

c) ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico



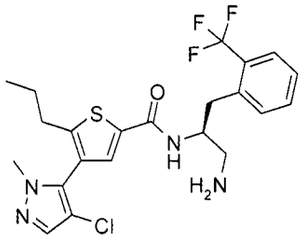
Una solución de 4-(1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (356 mg, 1,35 mmol) y N-clorosuccinimida (180 mg, 1,35 mmol) en tetrahidrofurano (6,7 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Se añadió en una porción hidróxido sódico 6 N (2,2 ml, 13,47 mmol) y la solución se agitó durante 12 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, produciendo ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico (357 mg, 1,25 mmol, rendimiento de 93%) en forma de un aceite de color amarillo: LCMS (ES) m/e 271, 273 (M, M+2)$^+$.

d) 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida



A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico (148 mg, 0,52 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (200 mg, 0,52 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,45 ml, 2,60 mmol) en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (267 mg, 0,57 mmol). La solución se agitó a 25ºC durante 12 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida (245 mg, 0,39 mmol, rendimiento de 75%) en forma de un aceite de color amarillo: LCMS (ES) m/e 615, 617 (M, M+2)$^+$.

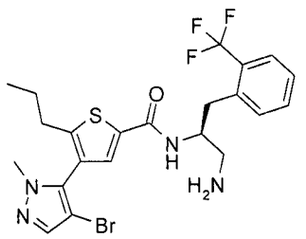
e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida



A una solución de 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida (245 mg, 0,40 mmol) en tetrahidrofurano (2,4 ml) y metanol (2,4 ml) a 25ºC se le añadió gota a gota hidrazina (0,12 ml, 3,98 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida (178 mg, 0,32 mmol, rendimiento de 80%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 485, 487 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,96 (s a, 1 H) 8,13 (s a, 3 H) 7,93 (s, 1 H) 7,66 - 7,73 (m, 2 H) 7,62 (s a, 1 H) 7,55 (t, J = 7,45 Hz, 1 H) 7,42 (t, J = 7,45 Hz, 1 H) 4,48 (s a, 1 H) 3,71 (s,

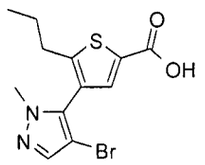
3 H) 2,99 - 3,08 (m, 4 H) 2,63 (t, *J* = 7,20 Hz, 2 H) 1,53 - 1,57 (m, 2 H) 0,83 (t, *J* = 7,33 Hz, 3 H).

Ejemplo 113



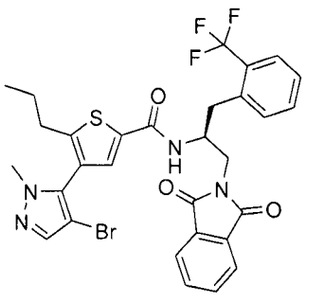
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida

a) ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico



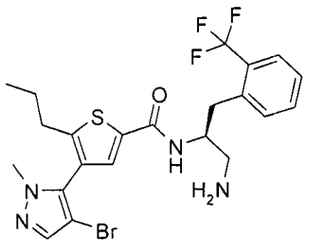
Una solución de 4-(1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (714 mg, 2,70 mmol) [preparado en el Ejemplo 112] y N-bromosuccinimida (481 mg, 2,70 mmol) en tetrahidrofurano (12 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. La mezcla de reacción se dividió y la mitad de la solución se trató con hidróxido sódico 6 N (2,251 ml, 13,51 mmol). La mezcla de reacción se agitó a 70°C en un tubo cerrado herméticamente durante 12 h y se repartió entre H_2O y DCM. El valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente, produciendo ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico (445 mg, 1,35 mmol, rendimiento de 50%): LCMS (ES) m/e 329, 331 (M, M+2)$^+$.

b) 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida



A una solución de ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico (171 mg, 0,52 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (200 mg, 0,52 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,45 ml, 2,60 mmol) en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (267 mg, 0,57 mmol). La solución se agitó a 25ºC durante 12 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida (251 mg, 0,37 mmol, rendimiento de 72%) en forma de un aceite de color amarillo: LCMS (ES) m/e 659,661 (M, M+2)$^+$.

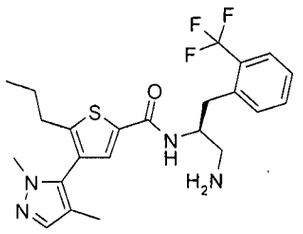
c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida



A una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida (251 mg, 0,38 mmol) en tetrahidrofurano (2,4 ml) y metanol (2,4 ml) a 25ºC se le añadió gota a gota hidrazina (0,12 ml, 3,81 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en

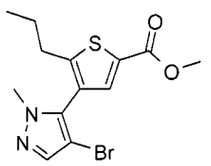
dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida (178 mg, 0,30 mmol, rendimiento de 78%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 529, 531 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,94 (d, J = 8,84 Hz, 1 H) 8,10 (s a, 3 H) 7,87 (d, J = 1,77 Hz, 1 H) 7,65 - 7,72 (m, 2 H) 7,58 (dd, J = 14,78, 7,71 Hz, 2 H) 7,43 (t, J = 7,45 Hz, 1 H) 4,48 (s a, 1 H) 3,71 (s, 3 H) 2,99 - 3,08 (m, 4 H) 2,58 - 2,66 (m, 2 H) 1,53 (ddd, J = 13,89, 6,82, 6,57 Hz, 2 H) 0,83 (dd, J = 7,33, 2,02 Hz, 3 H).

Ejemplo 114



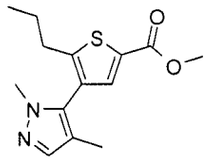
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo



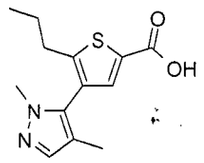
Una solución de 4-(1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (714 mg, 2,70 mmol) y N-bromosuccinimida (481 mg, 2,70 mmol) en tetrahidrofurano (12 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. La mezcla de reacción se dividió y la mitad se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente, produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (464 mg, 1,35 mmol, rendimiento de 50%) en forma de un aceite de color naranja: LCMS (ES) m/e 343, 345 (M, M+2)$^+$.

b) 4-(1,4-dimetil-1H-pirazol-5-il)-5-propiltiofeno-2-carboxilato de metilo



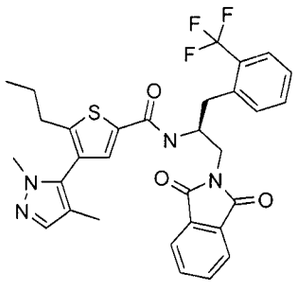
Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (242 mg, 0,71 mmol), $PdCl_2$(dppf) (52 mg, 0,07 mmol), carbonato potásico (487 mg, 3,53 mmol) y trimetilboroxina (0,20 ml, 1,41 mmol) en N,N-dimetilformamida (3,5 ml) se agitó a 110°C en un tubo cerrado herméticamente durante 2 h. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (184 mg, 0,60 mmol, rendimiento de 84%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 279 $(M+H)^+$.

c) ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-propiltiofeno-2-carboxílico



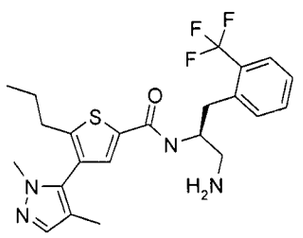
Una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxilato de metilo (0,184 g, 0,66 mmol) en hidróxido sódico 6 N (2,2 ml, 13,22 mmol) y tetrahidrofurano (6,6 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico (180 mg, 0,66 mmol, rendimiento de 100%) en forma de un aceite de color amarillo: LCMS (ES) m/e 265 $(M+H)^+$.

d) 4-(1,4-dimetil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[2-(trifluorometil)bencil]etil}-5-propiltiofeno-2-carboxamida



A una solución de ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxílico (180 mg, 0,68 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (262 mg, 0,68 mmol) [preparada en la Preparación 6] y diisopropiletilamina (0,59 ml, 3,40 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (350 mg, 0,75 mmol). La solución se agitó a 25°C durante 2 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida (243 mg, 0,41 mmol, rendimiento de 60%) en forma de un aceite de color amarillo: LCMS (ES) m/e 595 $(M+H)^+$.

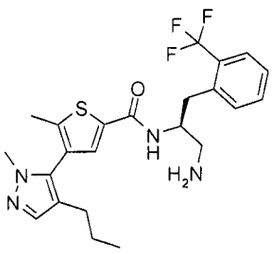
e) N-{(1S)-2-amino-1-[2-(trifluorometil)bencil]etil}-4-(1,4-dimetil-1H-pirazol-5-il)-5-propiltiofeno-2-carboxamida



A una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-propil-2-tiofenocarboxamida (243 mg, 0,41 mmol) en tetrahidrofurano (2 ml) y metanol (2 ml) a 25°C se le añadió gota a gota hidrazina (0,13 ml, 4,09 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se

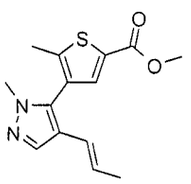
convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida (172 mg, 0,30 mmol, rendimiento de 74%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 465 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,80 (s a, 1 H) 8,08 (s a, 3 H) 7,78 (s, 1 H) 7,69 (d, *J* = 7,58 Hz, 1 H) 7,50 - 7,55 (m, 2 H) 7,43 (t, *J* = 7,71 Hz, 1 H) 7,37 (s, 1 H) 4,49 (d, *J* = 10,36 Hz, 1 H) 3,61 (s, 3 H) 2,99 - 3,06 (m, 4 H) 2,54 - 2,59 (m, 2 H) 1,87 (s, 3 H) 1,48 - 1,55 (m, 2 H) 0,81 (t, *J* = 7,33 Hz, 3 H).

Ejemplo 115



Preparación de N-{(1S)-2-amino-1-[2-(trifluorometil)bencil]etil}-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)tiofeno-2-carboxamida

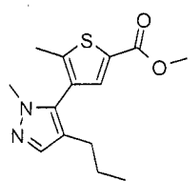
a) 5-metil-4-{1-metil-4-[(1E)-prop-1-en-1-il]-1H-pirazol-5-il}tiofeno-2-carboxilato de metilo



Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (320 mg, 1,015 mmol) [preparado en el Ejemplo 99], carbonato potásico (702 mg, 5,08 mmol), bis(tri-t-butilfosfina)paladio (0) (25,9 mg, 0,05 mmol) y ácido (1Z)-1-propen-1-ilborónico (87 mg, 1,01 mmol) en 1,4-dioxano (5,3 ml) y agua (1,3 ml) se agitó a 80ºC en un tubo cerrado herméticamente durante 12 h. Los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas

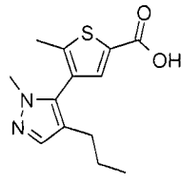
se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 5-metil-4-{1-metil-4-[(1Z)-1-propen-1-il]-1H-pirazol-5-il}-2-tiofenocarboxilato de metilo (243 mg, 0,88 mmol, rendimiento de 87%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 277 $(M+H)^+$.

b) 5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



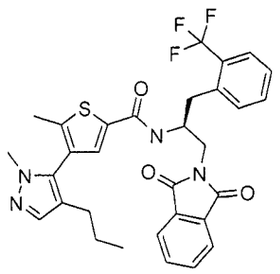
A una solución de 5-metil-4-{1-metil-4-[(1Z)-1-propen-1-il]-1H-pirazol-5-il}-2-tiofenocarboxilato de metilo (243 mg, 0,88 mmol) en metanol (6,8 ml) se le añadió $Pd(OH)_2$ (49 mg, 0,35 mmol). La mezcla de reacción se hidrogenó a 1 atm (globo) durante 1 h. Después, la solución se purgó con N_2, se filtró a través de Celite y se concentró, produciendo 5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (217 mg, 0,69 mmol, rendimiento de 78%) en forma de un aceite transparente que se usó sin purificación adicional: LCMS (ES) m/e 279 $(M+H)^+$.

c) ácido 5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxílico



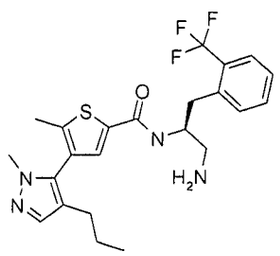
Una solución de 5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (217 mg, 0,78 mmol) en hidróxido sódico 6 N (2,60 ml, 15,59 mmol) y tetrahidrofurano (5,4 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxílico (242 mg, 0,78 mmol, rendimiento de 100%) en forma de una espuma de color blanco: LCMS (ES) m/e 265 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxílico (206 mg, 0,78 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (300 mg, 0,78 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,68 ml, 3,90 mmol) en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (400 mg, 0,86 mmol). La solución se agitó a 25ºC durante 12 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida (283 mg, 0,46 mmol, rendimiento de 60%) en forma de un aceite de color amarillo: LCMS (ES) m/e 595 $(M+H)^+$.

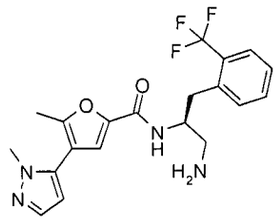
e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida (283 mg, 0,48 mmol) en tetrahidrofurano (2,4 ml) y metanol (2,4 ml) a 25ºC se le añadió gota a gota hidrazina (0,15 ml, 4,76 mmol). Después

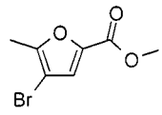
de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida (186 mg, 0,35 mmol, rendimiento de 73%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 465 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,81 (s a, 1 H) 8,13 (s a, 3 H) 7,79 (s, 1 H) 7,68 (d, J = 7,58 Hz, 1 H) 7,59 (d, J = 7,07 Hz, 1 H) 7,42 - 7,51 (m, 1 H) 7,38 - 7,45 (m, 2 H) 4,47 (s a, 1 H) 3,61 (d, J = 2,78 Hz, 3 H) 2,99 - 3,08 (m, 4 H) 2,25 (s, 3 H) 2,11 - 2,21 (m, 2 H) 1,41 - 1,48 (m, 2 H) 0,83 (s a, 3 H).

Ejemplo 116



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

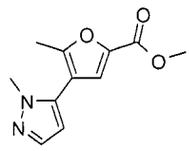
a) 4-bromo-5-metil-2-furanocarboxilato de metilo



A una solución de 5-metil-2-furanocarboxilato de metilo (1,5 g, 10,70 mmol) y tricloruro de aluminio (2,14 g, 16,06 mmol) en cloroformo (21 ml) a 0ºC se le añadió bromo (0,77 ml, 14,99 mmol). La solución resultante se agitó a 0ºC y se calentó a TA durante 12 h. Esta reacción se realizó en extracciones (1,5 g y 1 g) y las extracciones se combinaron, se añadieron a hielo y se repartieron entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 0,5-10% en hexanos), produciendo el

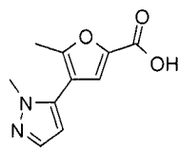
compuesto del título (2,1 g, 54%) en forma de un sólido de color blanco; LCMS (ES) m/z = 219, 221 (M, M+2)$^+$.

b) 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo



Una solución de 4-bromo-5-metil-2-furanocarboxilato de metilo (2,1 g, 9,59 mmol), carbonato potásico (6,63 g, 47,9 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,19 g, 10,55 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (0,24 g, 0,48 mmol) en 1,4-dioxano (40 ml) y agua (8 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 1 h. Se añadieron 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,19 g, 10,55 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,245 g, 0,48 mmol) y la reacción se agitó durante 1 h más y se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-40% en hexanos), produciendo 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (1,7 g, 7,72 mmol, rendimiento de 81%) en forma de un aceite de color amarillo: LCMS (ES) m/e 221 (M+H)$^+$.

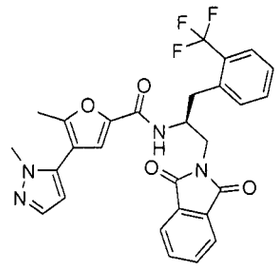
c) ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico



Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (200 mg, 0,91 mmol) en hidróxido sódico 6 N (2,3 ml, 13,62 mmol) y tetrahidrofurano (4,5 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-

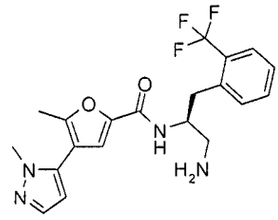
furanocarboxílico (130 mg, 0,57 mmol, rendimiento de 63%) en forma de un aceite de color amarillo: LCMS (ES) m/e 207 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida



A una solución de ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico (130 mg, 0,63 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (243 mg, 0,63 mmol) [preparada en la Preparación 6] y diisopropiletilamina (0,55 ml, 3,15 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (324 mg, 0,69 mmol). La solución se agitó a 25°C durante 12 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (190 mg, 0,23 mmol, rendimiento de 37%) en forma de un aceite transparente: LCMS (ES) m/e 537 $(M+H)^+$.

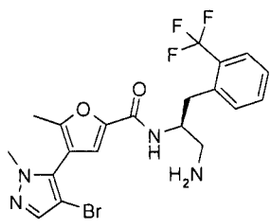
e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida



A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (190 mg, 0,35 mmol) en tetrahidrofurano (1,5 ml) y metanol (1,5 ml) a 25°C se le añadió gota a gota hidrazina (0,11 ml, 3,54 mmol). Después de 12 h la solución se

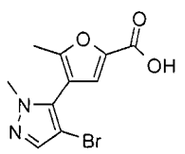
concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (71 mg, 0,15 mmol, rendimiento de 42%) en forma de un sólido de color amarillo: LCMS (ES) m/z 407 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 8,60 (d, J = 9,60 Hz, 1 H) 8,04 (s a, 3 H) 7,70 (d, J = 7,83 Hz, 1 H) 7,53 - 7,59 (m, 2 H) 7,49 (d, J = 1,77 Hz, 1 H) 7,38 - 7,45 (m, 2 H) 6,33 (s a, 1 H) 4,52 (s a, 1 H) 3,80 (s, 3 H) 2,98 - 3,09 (m, 4 H) 2,38 (s, 3 H).

Ejemplo 117:



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida

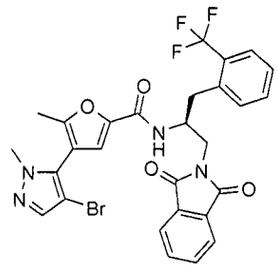
a) ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico



Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (600 mg, 2,72 mmol) [preparado en el Ejemplo 116] y n-bromosuccinimida (485 mg, 2,72 mmol) en tetrahidrofurano (13,6 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70ºC. La mezcla de reacción se dividió y la mitad de la solución se trató con hidróxido sódico 6 N (4,54 ml, 27,2 mmol), que se agitó a 70ºC en un tubo cerrado herméticamente durante 4 h. La solución se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4,

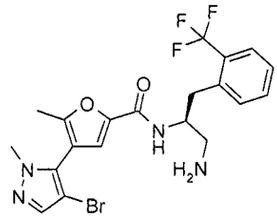
se concentraron y se usaron directamente, produciendo ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (369 mg, 1,29 mmol, rendimiento de 48%) en forma de un aceite de color naranja: LCMS (ES) m/e 285, 287 (M, M+2)$^+$.

b) 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida



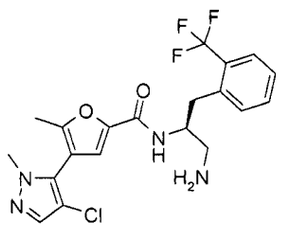
A una solución de ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (200 mg, 0,70 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (270 mg, 0,70 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,61 ml, 3,51 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (361 mg, 0,77 mmol). La solución se agitó a 25°C durante 1 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (232 mg, 0,32 mmol, rendimiento de 46%) en forma de un aceite transparente: LCMS (ES) m/e 615, 617 (M+H)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida



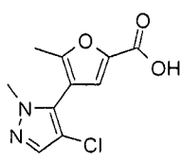
A una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (232 mg, 0,38 mmol) en tetrahidrofurano (2 ml) y metanol (2 ml) a 25ºC se le añadió gota a gota hidrazina (0,12 ml, 3,77 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida (106 mg, 0,19 mmol, rendimiento de 50%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 485, 487 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,60 (d, J = 9,60 Hz, 1 H) 7,99 (s a, 3 H) 7,68 (s, 2 H) 7,71 (d, J = 8,08 Hz, 1 H) 7,59 (d, J = 7,33 Hz, 1 H) 7,44 - 7,56 (m, 1 H) 7,25 - 7,33 (m, 1 H) 4,50 - 4,57 (m, 1 H) 3,74 (s, 3 H) 2,99 - 3,07 (m, 4 H) 2,32 (s, 3 H).

Ejemplo 118



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida

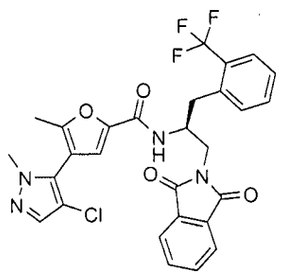
a) ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico



Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (300 mg, 1,36 mmol) y N-clorosuccinimida (182 mg, 1,36 mmol) en tetrahidrofurano (6,7 ml) se agitó en un tubo cerrado herméticamente durante 1 h a

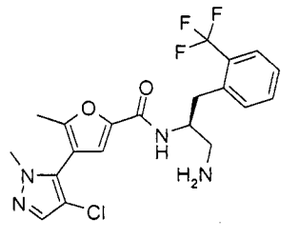
70°C. Se añadió en una porción hidróxido sódico 6 N (3,4 ml, 20,4 mmol) y la solución se agitó durante 12 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, produciendo ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (275 mg, 1,14 mmol, rendimiento de 84%) en forma de un aceite de color naranja: LCMS (ES) m/e 241, 243 $(M, M+2)^+$.

b) 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida



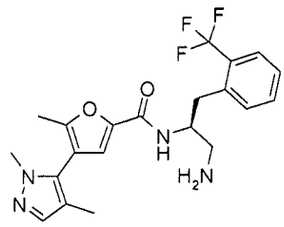
A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (200 mg, 0,83 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (320 mg, 0,83 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletilamina (0,72 ml, 4,16 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (427 mg, 0,91 mmol). La solución se agitó a 25°C durante 12 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (246 mg, 0,40 mmol, rendimiento de 49%) en forma de un aceite transparente: LCMS (ES) m/e 571, 573 $(M, M+2)^+$.

c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida



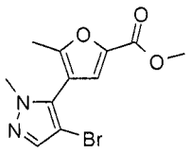
A una solución de 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (246 mg, 0,43 mmol) en tetrahidrofurano (2,1 ml) y metanol (2,1 ml) a 25ºC se le añadió gota a gota hidrazina (135 µl, 4,31 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida (125 mg, 0,24 mmol, rendimiento de 56%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,63 (d, J = 9,09 Hz, 1 H) 8,04 (s a, 3 H) 7,65 - 7,72 (m, 2 H) 7,59 (d, J = 7,33 Hz, 1 H) 7,57 (s a, 1 H) 7,39 - 7,47 (m, 1 H) 7,29 - 7,37 (m, 1 H) 4,54 (s a, 1 H) 3,73 (s, 3 H) 2,98 - 3,09 (m, 4 H) 2,33 (s, 3 H).

Ejemplo 119



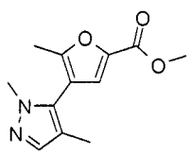
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida

a) 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo



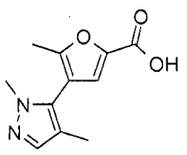
Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (600 mg, 2,72 mmol) [preparado en el Ejemplo 116] y N-bromosuccinimida (485 mg, 2,72 mmol) en tetrahidrofurano (13 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70ºC. La mezcla de reacción se dividió y la mitad de la solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 5-15% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo (130 mg, 0,41 mmol, rendimiento de 15%) en forma de un aceite de color naranja: LCMS (ES) m/e 299, 301 $(M, M+2)^+$.

b) 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo



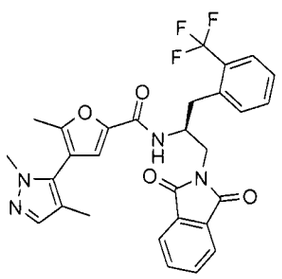
Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo (130 mg, 0,43 mmol) , carbonato potásico (300 mg, 2,17 mmol), $PdCl_2(dppf)$ (15,9 mg, 0,02 mmol) y trimetilboroxina (0,12 ml, 0,87 mmol) en N,N-dimetilformamida (3,5 ml) se agitó a 110ºC en un tubo cerrado herméticamente durante 2 h. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo (60 mg, 0,26 mmol, rendimiento de 59%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 235 $(M+H)^+$.

c) ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico



Una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo (60 mg, 0,26 mmol) en hidróxido sódico 6 N (0,8 ml, 5,1 mmol) y tetrahidrofurano (2,5 ml) se agitó a 70ºC en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (53 mg, 0,24 mmol, rendimiento de 94%) en forma de una espuma de color blanco: LCMS (ES) m/e 221 $(M+H)^+$.

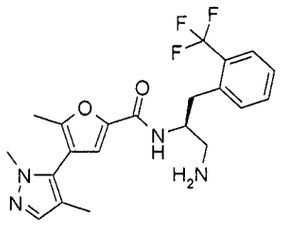
d) 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida



A una solución de ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (53 mg, 0,24 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (93 mg, 0,24 mmol) [preparada de acuerdo con la Preparación 6] y N,N-diisopropiletilamina (0,21 ml, 1,20 mmol) en diclorometano (2,4 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (124 mg, 0,26 mmol). La solución se agitó a 25ºC durante 1 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (113

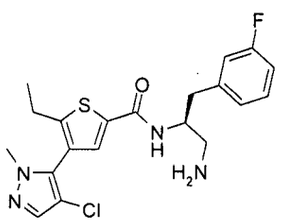
mg, 0,21 mmol, rendimiento de 85%) en forma de una espuma de color blanco: LCMS (ES) m/e 551 $(M+H)^+$.

e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida



A una solución de 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (113 mg, 0,21 mmol) en tetrahidrofurano (1 ml) y metanol (1 ml) a 25°C se le añadió gota a gota hidrazina (64 µl, 2,05 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida (32 mg, 0,06 mmol, rendimiento de 32%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 421 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,60 (d, J = 9,09 Hz, 1 H) 8,05 (s a, 3 H) 7,70 (d, J = 7,58 Hz, 1 H) 7,54 - 7,61 (m, 2 H) 7,40 - 7,47 (m, 1 H) 7,35 (s, 1 H) 7,27 (s, 1 H) 4,54 (s a, 1 H) 3,65 (s, 3 H) 2,98 - 3,07 (m, 4 H) 2,26 (s, 3 H) 1,90 (s, 3 H).

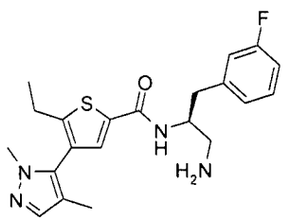
Ejemplo 120



Preparación de N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 100, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (155 mg, 0,46 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 421, 423 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,76 (s a, 1 H) 8,06 (s a, 3 H) 7,85 (s, 1 H) 7,69 (s, 1 H) 7,28 - 7,36 (m, 1 H) 7,12 (d, J = 7,07 Hz, 2 H) 7,03 (dd, J = 17,05, 2,15 Hz, 1 H) 4,36 (s a, 1 H) 3,69 (s, 3 H) 2,93 - 3,02 (m, 4 H) 2,67 (c, J = 7,33 Hz, 2 H) 1,16 (t, J = 7,45 Hz, 3 H).

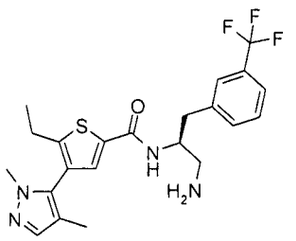
Ejemplo 121



N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 110, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (241 mg, 0,72 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 401 (M+H)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,76 (s a, 1 H) 8,11 (s a, 3 H) 7,79 (s, 1 H) 7,37 (s, 1 H) 7,28 – 7,36 (m, 1 H) 7,12 (d, J = 6,82 Hz, 2 H) 7,03 (td, J = 8,65, 1,64 Hz, 1 H) 4,41 – 4,43 (m, 1 H, oscurecido) 3,60 (s a, 3 H) 2,99 – 3,02 (m, 4 H) 2,60 (c, J = 7,33 Hz, 2 H) 1,86 (s, 3 H) 1,13 (t, J = 7,45 Hz, 3 H).

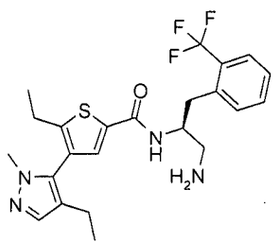
Ejemplo 122



Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida

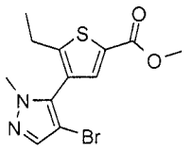
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 110, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (277 mg, 0,72 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 451 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,70 (s a, 1 H) 8,06 (s a, 3 H) 7,68 - 7,75 (m, 1 H) 7,52 (s, 1 H) 7,50 - 7,56 (m, 3 H) 7,37 (s, 1 H) 4,36 (d, *J* = 8,84 Hz, 1 H) 3,58 (s a, 3 H) 2,98 - 3,02 (m, 4 H) 2,55 - 2,61 (m, 2 H) 1,86 (s, 3 H) 1,12 (t, *J* = 7,58 Hz, 3 H).

Ejemplo 123



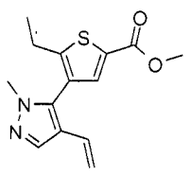
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo



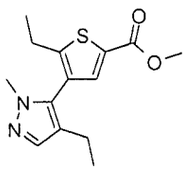
Una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (1 g, 3,99 mmol) [preparado en el Ejemplo 98] y N-bromosuccinimida (0,711 g, 3,99 mmol) en tetrahidrofurano (8 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (1,2 g, 3,54 mmol, rendimiento de 89%) en forma de un aceite de color naranja: LCMS (ES) m/e 329, 331 (M, M+2)$^+$.

b) 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo



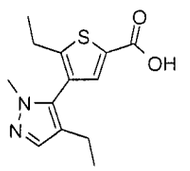
Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (300 mg, 0,911 mmol), carbonato potásico (630 mg, 4,56 mmol), bis(tri-t-butilfosfina)paladio (0) (23,29 mg, 0,05 mmol) y complejo de 2,4,6-trivinilcicloboroxano-piridina (110 mg, 0,45 mmol) en 1,4-dioxano (5 ml) y agua (1 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 2 h. Los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (187 mg, 0,66 mmol, rendimiento de 73%) en forma de un aceite transparente: LCMS (ES) m/z = 277 (M+H)$^+$.

c) 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



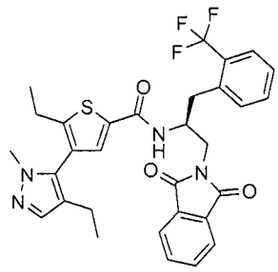
A una solución de 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (187 mg, 0,68 mmol) en metanol (2,5 ml) se le añadió Pd-C (7,20 mg, 0,07 mmol). La mezcla de reacción se hidrogenó a 1 atm (globo) durante 1 h. Después, la solución se purgó con N_2, se filtró a través de Celite y se concentró, produciendo 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (187 mg, 0,64 mmol, rendimiento de 95%) en forma de un aceite transparente que se usó sin purificación adicional: LCMS (ES) m/e 279 $(M+H)^+$.

d) ácido 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



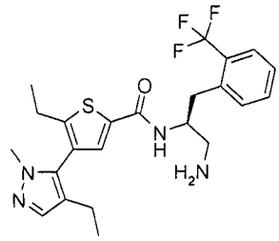
Una solución de 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (181 mg, 0,65 mmol) en hidróxido sódico 6 N (2,16 ml, 13,0 mmol) y tetrahidrofurano (5,4 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (175 mg, 0,65 mmol, rendimiento de 100%) en forma de una espuma de color blanco: LCMS (ES) m/e 265 $(M+H)^+$.

e) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (175 mg, 0,66 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (255 mg, 0,66 mmol) [preparada de acuerdo con el Procedimiento 6] y N,N-diisopropiletilamina (0,58 ml, 3,31 mmol) en diclorometano (4,6 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (340 mg, 0,73 mmol). La solución se agitó a 25°C durante 1 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (232 mg, 0,38 mmol, rendimiento de 57%) en forma de un aceite transparente: LCMS (ES) m/e 595 $(M+H)^+$.

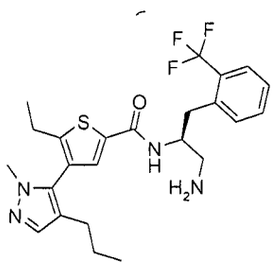
f) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (232 mg, 0,39 mmol) en tetrahidrofurano (2 ml) y metanol (2 ml) a 25°C se le añadió gota a gota hidrazina (122 µl, 3,90 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se

transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (176 mg, 0,38 mmol, rendimiento de 97%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 529, 531 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,64 (s a, 1 H) 7,97 (s a, 3 H) 7,65 - 7,73 (m, 3 H) 7,57 (d, *J* = 5,05 Hz, 2 H) 7,59 (s a, 1 H) 7,44 (s a, 1 H) 4,48 (s a, 1 H) 3,69 (s, 3 H) 2,98 - 3,12 (m, 4 H) 1,24 (dd, *J* = 6,82, 2,27 Hz, 3 H) 1,16 (dd, *J* = 6,82, 2,53 Hz, 3 H).

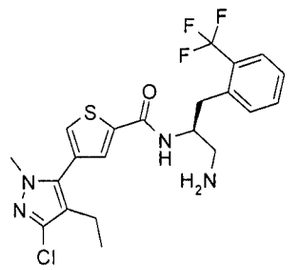
Ejemplo 124



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida

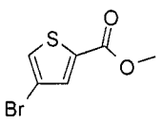
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 123, con la excepción de que se sustituyó complejo de 2,4,6-trivinilcicloboroxano-piridina por ácido (1Z)-1-propen-1-ilborónico (78 mg, 0,91 mmol): LCMS (ES) m/z = 479 (M+H)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,63 (s, 1 H) 8,01 (s a, 3 H) 7,67 (s, 2 H) 7,56 (d, *J* = 5,05 Hz, 2 H) 7,38 - 7,46 (m, 2 H) 4,42 - 4,47 (m, 1 H) 3,59 (s, 3 H) 2,98 - 3,02 (m, 4 H) 2,66 - 2,71 (m, 2 H) 1,40 - 1,47 (m, 2 H) 1,13 (t, *J* = 7,52 Hz, 3 H) 0,83 (t, *J* = 7,26 Hz, 3 H).

Ejemplo 125



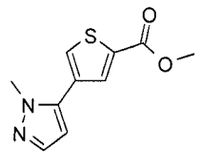
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) 4-bromo-2-tiofenocarboxilato de metilo



A una solución de ácido 4-bromo-2-tiofenocarboxílico (25 g, 121 mmol) en metanol (241 ml) se le añadió ácido sulfúrico (32 ml, 604 mmol). La solución resultante se agitó a 50°C durante 4 d. La solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, proporcionando 4-bromo-2-tiofenocarboxilato de metilo (26 g, 118 mmol, rendimiento de 97%), LCMS (ES) m/e 222 $(M+H)^+$.

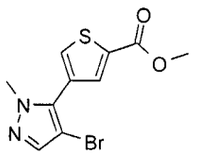
b) 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una solución de 4-bromo-2-tiofenocarboxilato de metilo (2,5 g, 11,31 mmol), carbonato potásico (7,81 g, 56,5 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,59 g, 12,44 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (0,289 g, 0,56 mmol) en 1,4-dioxano (47 ml) y agua (9 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 1 h. Se añadieron 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,59 g, 12,44 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,289 g, 0,56 mmol) y la

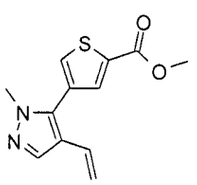
reacción se agitó durante 1 h más. La mezcla se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-40% en hexanos), produciendo 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,5 g, 11,25 mmol, rendimiento de 99%) en forma de un sólido de color amarillo: LCMS (ES) m/e 223 $(M+H)^+$.

c) 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una solución de 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,5 g, 11,25 mmol) y n-bromosuccinimida (2,002 g, 11,25 mmol) en tetrahidrofurano (56,2 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,7 g, 8,97 mmol, rendimiento de 80%) en forma de un sólido de color amarillo: LCMS (ES) m/e 301, 303 (M, M+2)$^+$.

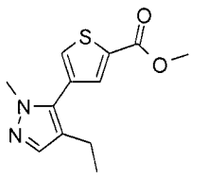
d) 4-(4-etenil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una solución de 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (300 mg, 0,91 mmol), carbonato potásico (630 mg, 4,56 mmol), bis(tri-t-butilfosfina)paladio (0) (23 mg, 0,05 mmol) y complejo de 2,4,6-trivinilcicloboroxano-piridina (110 mg, 0,46 mmol) en 1,4-dioxano (5 ml) y agua (1 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 2 h. Los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó

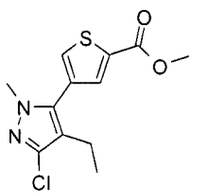
varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (187 mg, 0,66 mmol, rendimiento de 73%) en forma de un aceite transparente: LCMS (ES) m/z = 277 $(M+H)^+$.

e) 4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 4-(4-etenil-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (187 mg, 0,68 mmol) en metanol (2,5 ml) se le añadió Pd-C (7,20 mg, 0,07 mmol). La mezcla de reacción se hidrogenó a 1 atm (globo) durante 1 h. Después, la solución se purgó con N_2, se filtró a través de Celite y se concentró, produciendo 5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (187 mg, 0,64 mmol, rendimiento de 95%) en forma de un aceite transparente que se usó sin purificación adicional: LCMS (ES) m/e 279 $(M+H)^+$.

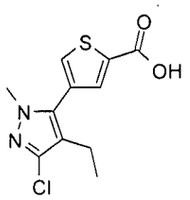
f) 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una solución de 4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (202 mg, 0,81 mmol) y NCS (108 mg, 0,81 mmol) en N,N-dimetilformamida (4 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 100ºC. Se añadió más cantidad de NCS (108 mg, 0,81 mmol) y la solución se agitó durante 1 h. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 2-30% en hexanos), produciendo 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato

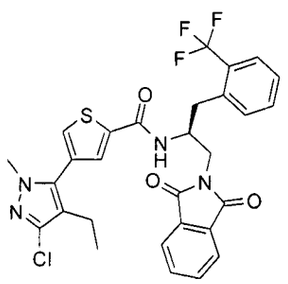
de metilo (135 mg, 0,45 mmol, rendimiento de 56%) en forma de un aceite de color amarillo: LCMS (ES) m/e 285 $(M+H)^+$.

g) ácido 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico



Una solución de 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (135 mg, 0,47 mmol) en hidróxido sódico 6 N (1,6 ml, 9,48 mmol) y tetrahidrofurano (5,4 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 12 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (120 mg, 0,41 mmol, rendimiento de 87%) en forma de una espuma de color blanco: LCMS (ES) m/e 270, 272 (M, M+2)$^+$.

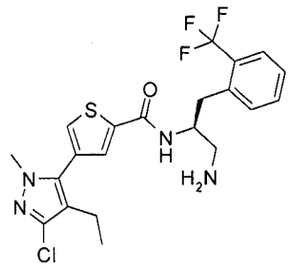
h) 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de ácido 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (120 mg, 0,44 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (171 mg, 0,44 mmol) [preparada de acuerdo con la Preparación 6] y N,N-diisopropiletilamina (0,39 ml, 2,22 mmol) en diclorometano (4,6 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (228 mg, 0,49 mmol). La solución se agitó a 25°C durante 1 h, después se cargó en seco sobre sílice y se

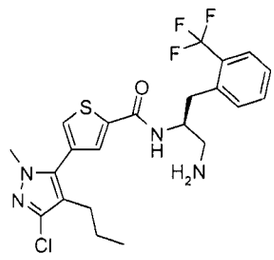
purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (190 mg, 0,30 mmol, rendimiento de 68%) en forma de un sólido de color blanco: LCMS (ES) m/e 601, 603 (M, M+2)$^+$.

i) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de 4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (190 mg, 0,32 mmol) en tetrahidrofurano (1,58 ml) y metanol (1,58 ml) a 25ºC se le añadió gota a gota hidrazina (0,08 ml, 2,53 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en éter (2 ml) en DCM (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (145 mg, 0,26 mmol, rendimiento de 83%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 471, 473 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,80 (s a, 1 H) 7,87 - 7,99 (m, 6 H) 7,69 (d, J = 7,71 Hz, 1H)) 7,57 (d, J = 7,83 Hz, 1 H) 7,40 - 7,44 (m, 1 H) 4,43 - 4,48 (m, 1 H) 3,74 (s, 3 H) 2,99 - 3,06 (m, 4 H) 2,40 (d, J = 7,58 Hz, 2 H) 1,04 (t, J = 7,58 Hz, 3 H).

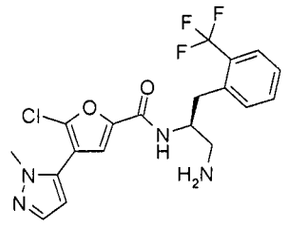
Ejemplo 126



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida

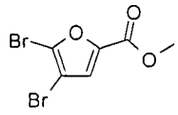
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 125, con la excepción de que se sustituyó complejo de 2,4,6-trivinilcicloboroxano-piridina por ácido (1Z)-1-propen-1-ilborónico (125 mg, 1,46 mmol): LCMS (ES) m/z = 485, 487 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,94 (d, *J* = 9,09 Hz, 1 H) 8,05 (s, 4 H) 7,98 (s, 1 H) 7,69 (d, *J* = 7,58 Hz, 1 H) 7,55 - 7,63 (m, 1 H) 7,52 (t, *J* = 7,58 Hz, 1 H) 7,42 (t, *J* = 7,33 Hz, 1 H) 4,49 (d, *J* = 4,29 Hz, 1 H) 3,74 (s, 3 H) 2,98 - 3,09 (m, 4 H) 2,37 (c, *J* = 7,07 Hz, 2 H) 1,37 - 1,45 (m, 2 H) 0,80 (t, *J* = 7,33 Hz, 3 H).

Ejemplo 127



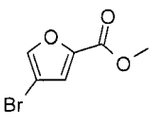
Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

a) 4,5-dibromo-2-furanocarboxilato de metilo



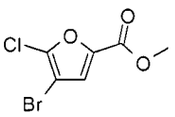
A una solución de ácido 4,5-dibromo-2-furanocarboxílico (25 g, 93 mmol) en metanol (185 ml) se le añadió ácido sulfúrico (24,7 ml, 463 mmol). La solución resultante se agitó a 50°C durante 12 h. La solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, proporcionando 4,5-dibromo-2-furanocarboxilato de metilo (23,67 g, 83 mmol, rendimiento de 90%), LCMS (ES) m/e 283, 285, 287 (M, M+2, $M+4)^+$.

b) 4-bromo-2-furanocarboxilato de metilo



A una solución de 4,5-dibromo-2-furanocarboxilato de metilo (3,3 g, 11,62 mmol) en tetrahidrofurano (46 ml) a -40°C se le añadió cloruro de isopropilmagnesio (6,97 ml, 13,95 mmol). Después de 1 h, se añadió agua (11 ml) y la solución se calentó a 25°C. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 3% en hexanos), produciendo 4-bromo-2-furanocarboxilato de metilo (1,4 g, 6,49 mmol, rendimiento de 56%) en forma de un sólido de color amarillo: LCMS (ES) m/e 205, 207 (M, $M+2)^+$.

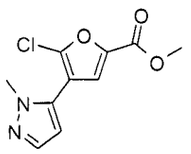
c) 4-bromo-5-cloro-2-furanocarboxilato de metilo



Una solución de 4-bromo-2-furanocarboxilato de metilo (1,4 g, 6,83 mmol) y NCS (0,912 g, 6,83 mmol) en N,N-dimetilformamida (13,7 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 100°C. Después de 1 h, la solución se repartió entre DCM-H_2O y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 2-10% en hexanos), produciendo 4-bromo-5-cloro-2-furanocarboxilato de metilo (1,348 g, 5,12 mmol,

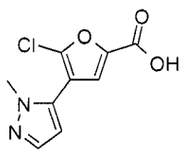
rendimiento de 75%) en forma de un sólido de color blanco: LCMS (ES) m/e 238, 240, 242 (M, M+2, M+4)$^+$.

d) 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo



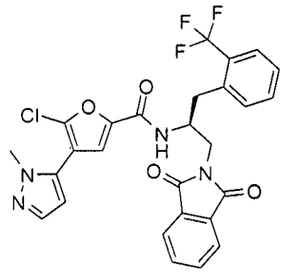
Una solución de 4-bromo-5-cloro-2-furanocarboxilato de metilo (1,1 g, 4,59 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,05 g, 5,05 mmol) [preparado de acuerdo con la Preparación 7], carbonato potásico (3,17 g, 22,97 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,117 g, 0,23 mmol) en 1,4-dioxano (19,14 ml) y agua (3,83 ml) se agitó a 80ºC en un tubo cerrado herméticamente durante 1 h. La mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 4-25% en hexanos), produciendo 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (800 mg, 2,53 mmol, rendimiento de 55%) en forma de un aceite de color amarillo: LCMS m/e ES 240, 242 (M, M+2)$^+$.

e) ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico



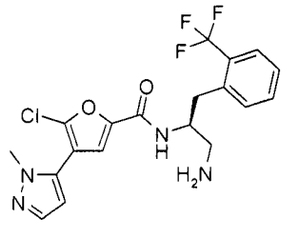
Una solución de 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (300 mg, 1,25 mmol) en hidróxido sódico 6 N (4,16 ml, 24,93 mmol) y tetrahidrofurano (5,4 ml) se agitó a 70ºC en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico (267 mg, 0,59 mmol, rendimiento de 47%) en forma de una espuma de color blanco: LCMS (ES) m/e 265 (M+H)$^+$.

f) 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida



A una solución de ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico (134 mg, 0,59 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (228 mg, 0,59 mmol) [preparada de acuerdo con la Preparación 6] y N,N-diisopropiletilamina (0,52 ml, 2,96 mmol) en diclorometano (4,6 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (304 mg, 0,65 mmol). La solución se agitó a 25°C durante 1 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (202 mg, 0,33 mmol, rendimiento de 55,8%) en forma de un aceite de color amarillo: LCMS (ES) m/e 557, 559 (M, M+2)$^+$.

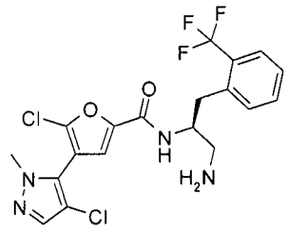
g) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida



A una solución de 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (202 mg, 0,36 mmol) en tetrahidrofurano (1,8 ml) y metanol (1,8 ml) a 25°C se le añadió gota a gota hidrazina (0,08 ml, 2,54 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 2% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl

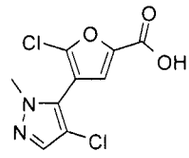
mediante la adición al residuo de un exceso de HCl 2 M en éter dietílico (2 ml) en DCM (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida (120 mg, 0,24 mmol, rendimiento de 66%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 427, 429 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,87 (d, J = 9,09 Hz, 1 H) 8,11 (s a, 3 H) 7,66 - 7,73 (m, 2 H) 7,57 (t, J = 7,45 Hz, 2 H) 7,53 (d, J = 1,52 Hz, 1 H) 7,44 (d, J = 6,82 Hz, 1 H) 6,50 (d, J = 1,52 Hz, 1 H) 4,43 - 4,51 (m, 1 H) 3,86 (s, 3 H) 2,99 - 3,17 (m, 4H).

Ejemplo 128



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida

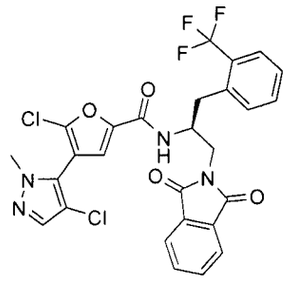
a) ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxílico



Una solución de 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (300 mg, 1,25 mmol) [preparado de acuerdo con el Ejemplo 127] y n-clorosuccinimida (166 mg, 1,25 mmol) en tetrahidrofurano (6 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Se añadió en una porción hidróxido sódico 6 N (4,1 ml, 24,94 mmol) y la solución se agitó durante 12 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se usaron directamente sin purificación adicional, produciendo ácido 5-cloro-4-(4-cloro-1-metil-

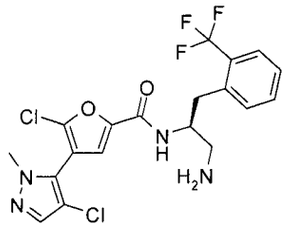
1H-pirazol-5-il)-2-furanocarboxílico (232 mg, 0,44 mmol, rendimiento de 36%) en forma de un aceite de color amarillo: LCMS (ES) m/e 261, 263 (M, M+2)$^+$.

b) 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-furanocarboxamida



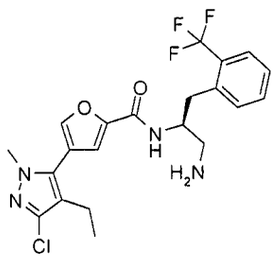
A una solución de ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxílico (116 mg, 0,44 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (171 mg, 0,44 mmol) [preparada de acuerdo con la Preparación 6] y N,N-diisopropiletilamina (0,39 ml, 2,22 mmol) en diclorometano (4,6 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (228 mg, 0,49 mmol). La solución se agitó a 25ºC durante 1 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-furanocarboxamida (116 mg, 0,19 mmol, rendimiento de 42%) en forma de un aceite de color amarillo: LCMS (ES) m/e 591, 593 (M, M+2)$^+$.

c) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida



A una solución de 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-furanocarboxamida (116 mg, 0,20 mmol) en tetrahidrofurano (1 ml) y metanol (1 ml) a 25°C se le añadió gota a gota hidrazina (0,04 ml, 1,37 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 2% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 2 M en éter (2 ml) en DCM (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida (68 mg, 0,13 mmol, rendimiento de 65%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,80 (d, J = 9,09 Hz, 1 H) 8,03 (s a, 3 H) 7,66 - 7,73 (m, 2 H) 7,58 - 7,61 (m, 1 H) 7,52 - 7,59 (m, 2 H) 7,40 - 7,48 (m, 1 H) 4,5 - 4,57 (m, 1 H) 3,77 (s, 3 H) 2,98 - 3,09 (m, 4 H).

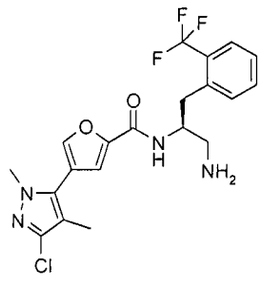
Ejemplo 129



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 125, con la excepción de que se sustituyó 4-bromo-2-tiofenocarboxilato de metilo por 4-bromo-2-furanocarboxilato de metilo (5 g, 24,39 mmol): LCMS (ES) m/z = 455, 457 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,75 (d, J = 9,09 Hz, 1 H) 8,23 (s, 1 H) 8,05 (s a, 3 H) 7,70 (d, J = 7,83 Hz, 1 H) 7,53 - 7,60 (m, 2 H) 7,42=0 - 7,43 (m, 2 H) 4,50 - 4,55 (m, 1 H) 3,74 (s, 3 H) 2,99 - 3,08 (m, 4 H) 2,39 (c, J = 7,33 Hz, 2 H) 1,03 (t, J = 7,45 Hz, 3 H).

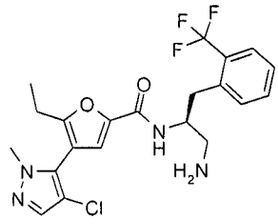
Ejemplo 130



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida

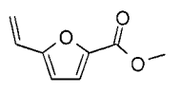
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 125, con la excepción de que se sustituyó complejo de 2,4,6-trivinilcicloboroxano-piridina por trimetilboroxina (0,78 ml, 5,61 mmol) y 4-bromo-2-tiofenocarboxilato de metilo por 4-bromo-2-furanocarboxilato de metilo (5 g, 24,39 mmol): LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,71 (d, J = 9,35 Hz, 1 H) 8,27 (s, 1 H) 8,01 (s a, 3 H) 7,70 (d, J = 7,58 Hz, 1 H) 7,55 (t, J = 6,06 Hz, 2 H) 7,40 - 7,47 (m, 2 H) 4,50 - 4,57 (m, 1 H) 3,78 (s, 3 H) 2,99 - 3,08 (m, 4 H) 1,98 (s, 3 H).

Ejemplo 131:



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida

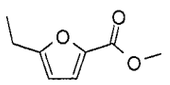
a) 5-etenil-2-furanocarboxilato de metilo



Una solución de 5-bromo-2-furanocarboxilato de metilo (2,5 g, 12,19 mmol), carbonato potásico (8,43 g, 61,0 mmol), bis(tri-t-butilfosfina)paladio (0) (0,312 g,

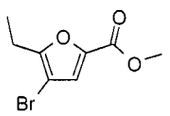
0,61 mmol) y complejo de 2,4,6-trivinilcicloboroxano-piridina (1,47 g, 6,10 mmol) en 1,4-dioxano (50 ml) y agua (10 ml) se agitó a 80ºC en un tubo cerrado herméticamente durante 2 h. Los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 5-etenil-2-furanocarboxilato de metilo (1,3 g, 7,09 mmol, rendimiento de 58%) en forma de un aceite de color amarillo: LCMS (ES) m/z = 153 $(M+H)^+$.

b) 5-etil-2-furanocarboxilato de metilo



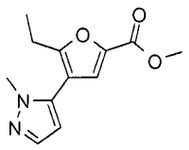
A una solución de 5-etenil-2-furanocarboxilato de metilo (1,3 g, 8,54 mmol) en metanol (15 ml) se le añadió $PdOH_2$ (0,240 g, 1,71 mmol). La mezcla de reacción se hidrogenó a 1 atm (globo) durante 1 h. Después, la solución se purgó con N_2, se filtró a través de Celite y se concentró, produciendo 5-etil-2-furanocarboxilato de metilo (1,2 g, 7,16 mmol, rendimiento de 84%) en forma de un aceite transparente que se usó sin purificación adicional: LCMS (ES) m/e 155 $(M+H)^+$.

c) 4-bromo-5-etil-2-furanocarboxilato de metilo



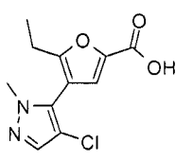
A una solución de 5-etil-2-furanocarboxilato de metilo (1,2 g, 7,78 mmol) y tricloruro de aluminio (1,56 g, 11,68 mmol) en cloroformo (15 ml) a 25ºC se le añadió bromo (0,56 ml, 10,90 mmol). La solución resultante se agitó a 70ºC en un tubo cerrado herméticamente durante 2 h y la solución se enfrió, se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 5% en hexanos), produciendo 4-bromo-5-etil-2-furanocarboxilato de metilo (1,1 g, 3,26 mmol, rendimiento de 41,8%) en forma de un sólido de color blanco; LCMS (ES) m/z = 233, 235 $(M, M+2)^+$.

d) 5-etil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo



Una solución de 4-bromo-5-etil-2-furanocarboxilato de metilo (1,1 g, 4,72 mmol), carbonato potásico (3,26 g, 23,60 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,178 g, 5,66 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (0,121 g, 0,24 mmol) se combinaron en un tubo cerrado herméticamente y la mezcla se agitó a 80°C durante 1 h. El análisis por LCMS mostró 4:1 de pdt/mp. Se añadieron más cantidad 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,178 g, 5,66 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,121 g, 0,24 mmol) y la solución se agitó durante 2 h más mientras permanecía en bruto. El análisis por LCMS mostró la conversión casi completa en el producto. Después, los contenidos de la reacción se repartieron entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo 5-etil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (950 mg, 3,37 mmol, rendimiento de 71,3%) en forma de un aceite de color amarillo: LCMS (ES) m/e 235 $(M+H)^+$.

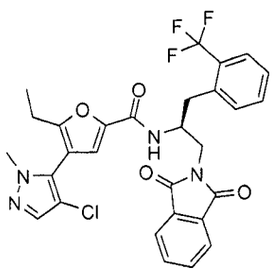
e) ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxílico



Una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (950 mg, 4,06 mmol) y N-clorosuccinimida (542 mg, 4,06 mmol) en tetrahidrofurano (20 ml) se agitó en un tubo cerrado herméticamente durante 1 h a 70°C. Se añadió en una porción hidróxido sódico 6 N (13,5 ml, 81 mmol) y la solución se agitó durante 1 h más. Después, la mezcla de reacción se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4 y se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4,

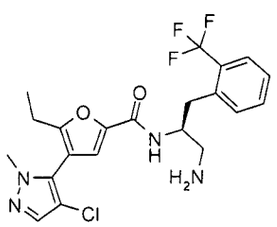
se concentraron y se usaron directamente sin purificación adicional, produciendo ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxílico (683 mg, 2,55 mmol, rendimiento de 62,8%) en forma de un aceite de color amarillo: LCMS (ES) m/e 254, 256 (M, M+2)$^+$.

f) 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-furanocarboxamida



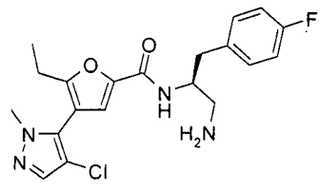
A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxílico (145 mg, 0,57 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (219 mg, 0,57 mmol) [preparada de acuerdo con la Preparación 6] y N,N-diisopropiletilamina (0,50 ml, 2,85 mmol) en diclorometano (4,6 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (292 mg, 0,63 mmol). La solución se agitó a 25ºC durante 1 h, después se cargó en seco sobre sílice y se purificó por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-furanocarboxamida (250 mg, 0,41 mmol, rendimiento de 71%) en forma de un sólido de color blanco: LCMS (ES) m/e 585, 587 (M, M+2)$^+$.

g) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida



A una solución de 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-2-furanocarboxamida (250 mg, 0,43 mmol) en tetrahidrofurano (1,8 ml) y metanol (1,8 ml) a 25°C se le añadió gota a gota hidrazina (0,13 ml, 4,27 mmol). Después de 12 h la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 2% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 2 M en éter (2 ml) en DCM (2 ml), produciendo la sal HCl de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida (166 mg, 0,30 mmol, rendimiento de 70%) en forma de un sólido de color amarillo: LCMS (ES) m/z = 455, 457 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,59 (s a, 1 H) 8,06 (s a, 3 H) 7,67 (s, 1 H) 7,70 (d, *J* = 7,83 Hz, 1 H) 7,59 (d, *J* = 4,29 Hz, 2 H) 7,44 (d, *J* = 4,04 Hz, 1 H) 7,31 (d, *J* = 5,81 Hz, 1 H) 4,50 - 4,57 (m, 1 H) 3,72 (s, 3 H) 2,99 - 3,12 (m, 4 H) 2,63 (c, *J* = 7,33 Hz, 2 H) 1,21 (t, *J* = 7,45 Hz, 3 H).

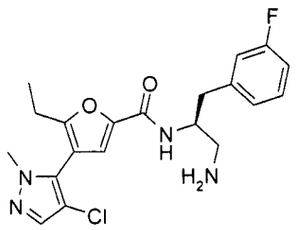
Ejemplo 132



Preparación de N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 131, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (170 mg, 0,57 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 405, 407(M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d6) ppm 8,56 (d, J = 8,59 Hz, 1 H) 8,09 (s a, 3 H) 7,67 (s, 1 H) 7,33 (s, 1 H) 7,31 (dd, J = 8,34, 5,81 Hz, 2 H) 7,12 (t, J = 8,72 Hz, 2 H) 4,36 - 4,39 (m, 1 H) 3,71 (s, 3 H) 2,91 - 3,03 (m, 4 H) 2,62 (c, J = 7,58 Hz, 2 H) 1,20 (t, J = 7,45 Hz, 3 H).

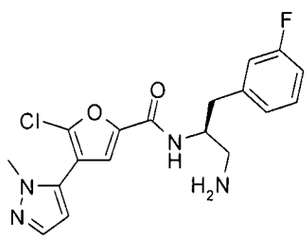
Ejemplo 133



Preparación de N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el Ejemplo 131, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (170 mg, 0,57 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 405, 407 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 8,62 (d, J = 8,59 Hz, 1 H) 8,13 (s a, 3 H) 7,67 (s, 1 H) 7,30 - 7,37 (m, 2 H) 7,12 (d, J = 6,32 Hz, 2 H) 7,04 (t, J = 8,59 Hz, 1 H) 4,40 - 4,47 (m, 1 H) 3,71 (s, 3 H) 2,95 - 3,09 (m, 4 H) 2,62 (c, J = 7,07 Hz, 2 H) 1,20 (t, J = 7,33 Hz, 3 H).

Ejemplo 134

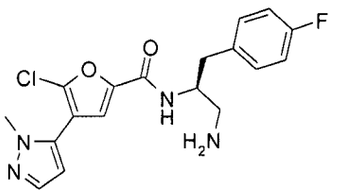


Preparación de N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de una espuma de color blanco de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (295 mg,

0,88 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 377, 379 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,87 (d, J = 8,84 Hz, 1 H) 8,16 (s a, 3 H) 7,70 - 7,77 (m, 1 H) 7,53 (d, J = 1,77 Hz, 1 H) 7,32 (t, J = 7,20 Hz, 1 H) 7,09 - 7,14 (m, 1 H) 7,11 (d, J = 6,57 Hz, 2 H) 7,04 (t, J = 8,59 Hz, 1 H) 6,49 (d, J = 1,77 Hz, 1 H) 4,41 - 4,44 (m, 1 H) 3,86 (s, 3 H) 2,95 - 3,00 (m, 4 H).

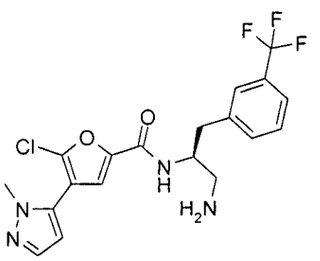
Ejemplo 135



Preparación de N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de una espuma de color blanco de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (295 mg, 0,88 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 377, 379 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,80 (d, J = 8,84 Hz, 1 H) 8,11 (s a, 3 H) 7,71 (s, 1 H) 7,53 (d, J = 1,77 Hz, 1 H) 7,29 (dd, J = 8,59, 5,56 Hz, 2 H) 7,12 (t, J = 8,84 Hz, 2 H) 6,49 (d, J = 1,77 Hz, 1 H) 4,32 - 4,38 (m, 1 H) 3,86 (s, 3 H) 2,99 - 3,01 (m, 4 H).

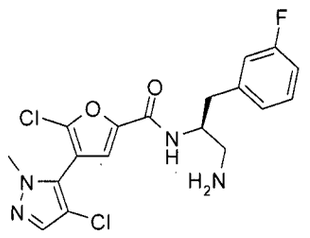
Ejemplo 136



Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de una espuma de color blanco de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (340 mg, 0,88 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 427, 429 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,83 (d, *J* = 8,84 Hz, 1 H) 8,11 (s a, 3 H) 7,62 - 7,69 (m, 2 H) 7,51 - 7,59 (m, 4 H) 6,48 (d, *J* = 1,77 Hz, 1 H) 4,39 - 4,44 (m, 1 H) 3,85 (s, 3 H) 2,97 - 3,05 (m, 4 H).

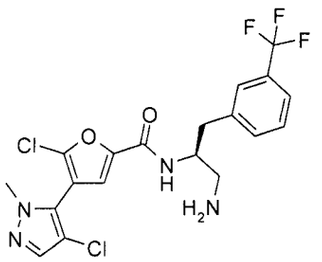
Ejemplo 137



Preparación de N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de una espuma de color blanco de acuerdo con el procedimiento del Ejemplo 128, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (321 mg, 0,96 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 411, 413 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,77 (d, *J* = 8,84 Hz, 1 H) 8,04 (s a, 3 H) 7,72 (s, 1 H) 7,59 (s, 1 H) 7,30 - 7,38 (m, 1 H) 7,11 (d, *J* = 7,58 Hz, 2 H) 7,05 (t, *J* = 8,59 Hz, 1 H) 4,39 - 4,43 (m, 1 H) 3,77 (s, 3 H) 2,97 - 3,03 (m, 4 H).

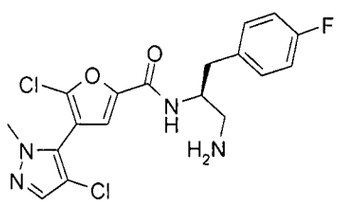
Ejemplo 138



Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de una espuma de color blanco de acuerdo con el procedimiento del Ejemplo 128, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (221 mg, 0,58 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 461, 463 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,83 (d, J = 8,84 Hz, 1 H) 8,10 (s a, 3 H) 7,72 (s, 1 H) 7,64 (s, 1 H) 7,52 - 7,60 (m, 4 H) 4,39 - 4,41 (m, 1 H) 3,76 (s, 3 H) 2,98 - 3,05 (m, 4 H).

Ejemplo 139:

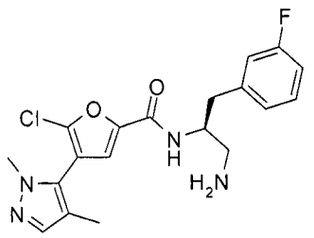


Preparación de N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de una espuma de color blanco de acuerdo con el procedimiento del Ejemplo 128, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (256 mg, 0,77 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 411, 413 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,78 (d, J = 8,59 Hz, 1 H) 8,06 (s a, 3 H) 7,72 (s, 1 H) 7,60 (s, 1 H) 7,30 (dd, J = 8,59, 5,56

Hz, 2 H) 7,13 (t, *J* = 8,84 Hz, 2 H) 4,35 - 4,42 (m, 1 H) 3,77 (s, 3 H) 2,99 (s a, 2 H) 2,86 - 2,93 (m, 2 H).

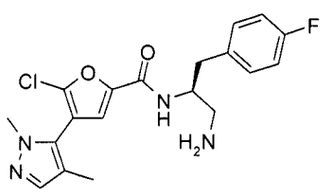
Ejemplo 140



Preparación de N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,02 g, 4,59 mmol) [preparado de acuerdo con la Preparación 17] y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (132 mg, 0,39 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 391, 393 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,75 (d, *J* = 8,84 Hz, 1 H) 8,04 (s a, 3 H) 7,55 (s, 1 H) 7,37 (s, 1 H) 7,30 - 7,36 (m, 1 H) 7,11 - 7,15 (m, 2 H) 7,05 - 7,10 (m, 1 H) 4,42 (s a, 1 H) 3,70 (s, 3 H) 2,97 (s a, 2 H) 2,92 - 2,96 (m, 2 H) 1,94 (s, 3 H).

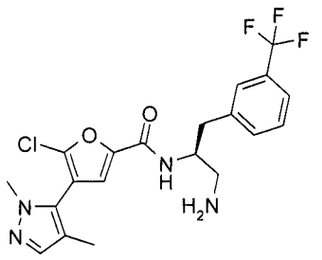
Ejemplo 141



Preparación de N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (3,06 g, 13,78 mmol) [preparado de acuerdo con la Preparación 17] y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (174 mg, 0,52 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 391, 393 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,81 (d, J = 8,59 Hz, 1 H) 8,14 (s a, 3 H) 7,59 (s, 1 H) 7,37 (s, 1 H) 7,30 (dd, J = 8,59, 5,56 Hz, 2 H) 7,12 (t, J = 8,84 Hz, 2 H) 4,32 - 4,38 (m, 1 H) 3,70 (s, 3 H) 2,98 (d, J = 5,81 Hz, 2 H) 2,91 (d, J = 6,32 Hz, 2 H) 1,94 (s, 3 H).

Ejemplo 142

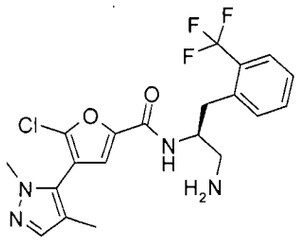


Preparación de N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (3,06 g, 13,78 mmol) [preparado de acuerdo con la Preparación 17] y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (200 mg, 0,52 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,83 (s a, 1 H) 8,15 (s a,

2 H) 7,63 (s a, 1 H) 7,52 - 7,58 (m, 4 H) 7,37 (s, 1 H) 4,38 - 4,42 (m, 1 H) 3,68 (s, 3 H) 2,97 - 3,08 (m, 4 H) 1,93 (s, 3 H).

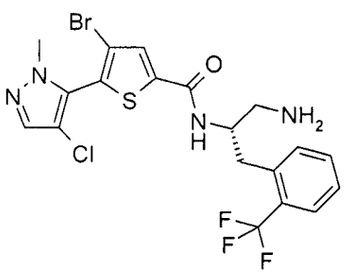
Ejemplo 143



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida

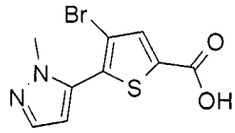
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol por 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (3,06 g, 13,78 mmol) [preparado de acuerdo con la Preparación 17] y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (200 mg, 0,52 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LCMS (ES) m/z = 441, 443 (M, M+2)$^+$, ^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 8,87 (d, J = 9,35 Hz, 1 H) 8,11 (s a, 3 H) 7,70 (d, J = 7,83 Hz, 1 H) 7,52 - 7,57 (m, 3 H) 7,41 - 7,47 (m, 1 H) 7,38 (s, 1 H) 4,39 - 4,43 (m, 1 H) 3,71 (s, 3 H) 2,98 - 3,09 (m, 4 H) 1,95 (s, 3 H).

Ejemplo 144



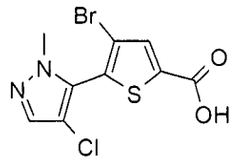
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



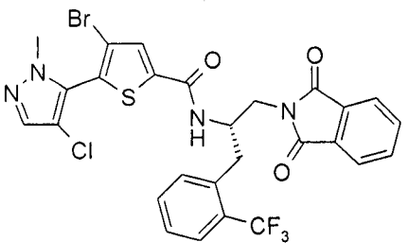
A una solución de ácido 4,5-dibromo-2-tiofenocarboxílico (3,30 g, 11,54 mmol) en dioxano/H_2O (4:1, 100 ml) se le añadieron K_2CO_3 (5,5 g, 40,0 mmol), tetraquistrifenilfosfina Pd(0) (671 mg, 0,58 mmol) y 5-(5,5-dimetil-1,3,2-dioxaborinan-2-il)-1-metil-1*H*-pirazol (2,66 g, 13,71 mmol). La mezcla de reacción se calentó a 80ºC en un tubo cerrado herméticamente durante 12 horas. La mezcla de reacción se repartió entre H_2O y $CHCl_3$. El valor del pH de la fase acuosa se ajustó a ~3 con HCl 6 N y se lavó varias veces con $CHCl_3$. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional (3,3 g, cuant.): LC-MS (ES) m/z = 289 $(M+H)^+$.

b) ácido 4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



Se añadió en porciones N-clorosuccinimida (NCS) (299 mg, 2,194 mmol) a un tubo reactor cerrado herméticamente de 30 ml que contenía ácido 4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (503 mg, 1,23 mmol) en tetrahidrofurano (THF) (6 ml) a temperatura ambiente. La mezcla se calentó a 70ºC durante 2 horas. Después de que se completara, la mezcla de reacción se repartió entre $CHCl_3$ y H_2O, la capa orgánica se secó con Na_2SO_4 y los disolventes se retiraron por destilación al vacío produciendo el compuesto del título (0,54 mg, cuant.) que se usó sin purificación adicional. LC-MS (ES) m/z = 321 $(M+H)^+$

c) 4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



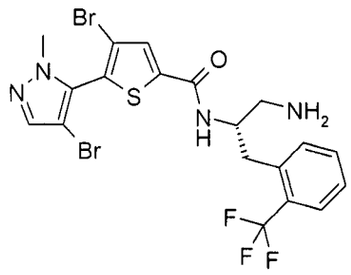
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-bromo-5-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (224 mg, 0,52 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (201 mg, 0,52 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y PyBrop (295 mg, 0,63 mmol) en cloroformo (4 ml). Se añadió DIEA (0,46 ml, 2,63 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (hexanos/EtOAc), produciendo el compuesto del título (153 mg, 43%): LC-MS (ES) m/z = 651 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-bromo-5-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (153 mg, 0,223 mmol) en tetrahidrofurano (THF) (2,5 ml) y metanol (0,5 ml). Se añadió hidrazina (50 µl, 1,59 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. Después de que se completara, la mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

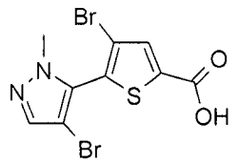
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (68 mg, 0,11 mmol, rendimiento de 48,7%): LC-MS (ES) m/z = 523 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 3,02 - 3,14 (m, 4 H) 3,73 (s, 3 H) 4,50 (s, 1 H) 7,40 - 7,48 (m, 1 H) 7,56 - 7,64 (m, 2 H) 7,71 (d, *J* = 7,83 Hz, 1 H) 7,77 (s, 1 H) 8,14 (s, 3 H) 8,21 (s, 1 H) 9,24 (d, *J* = 9,09 Hz, 1 H).

Ejemplo 145



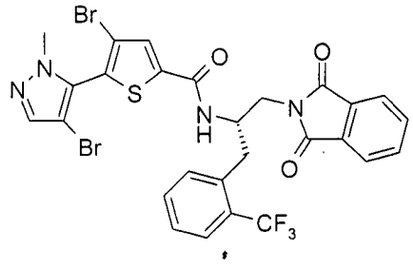
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-bromo-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



El compuesto del título se preparó de acuerdo con el procedimiento del Ejemplo 144 con la excepción de que se sustituyó NCS por N-bromosuccinimida (NBS) (287 mg, 1,596 mmol): LC-MS (ES) m/z = 364 $(M+H)^+$.

b) 4-bromo-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-bromo-5-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (238 mg, 0,52 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (209 mg, 0,54 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y PyBrop (293 mg, 0,63 mmol) en cloroformo (4 ml). Se añadió DIEA (0,46 ml, 2,62 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (sílice)

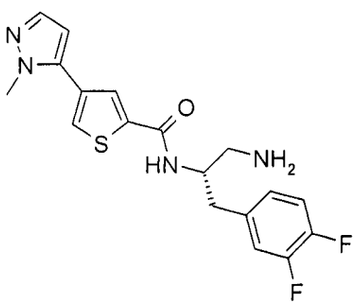
(3:1 de hex/EtOAc), produciendo el compuesto del título (229 mg, 60%): LC-MS (ES) m/z = 695 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadieron 4-bromo-5-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (229 mg, 0,312 mmol) en tetrahidrofurano (THF) (2,5 ml) y metanol (0,5 ml). Se añadió hidrazina (60 µl, 1,91 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH; columna de 12 g).

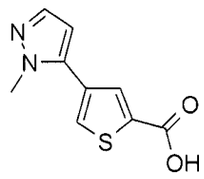
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O (500 ml) y se concentró, produciendo la sal HCl del compuesto del título (104 mg, 0,15 mmol, rendimiento de 49%): LC-MS (ES) m/z = 567 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 3,10 (s, 4 H) 3,74 (s, 3 H) 4,50 (s, 1 H) 7,45 (ddd, *J* = 7,96, 4,17, 4,04 Hz, 1 H) 7,60 (d, *J* = 4,04 Hz, 2 H) 7,71 (d, *J* = 7,58 Hz, 1 H) 7,76 (s, 1 H) 8,11 (s, 3 H) 8,19 (s, 1 H) 9,19 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 146



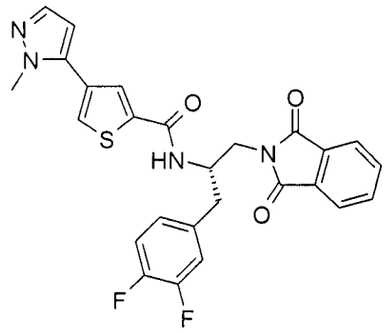
Preparación de N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A una solución de ácido 4-bromo-2-tiofenocarboxílico (3,91 g, 18,9 mmol) en dioxano/H_2O (4:1, 100 ml) se le añadieron Cs_2CO_3 (21,7 g, 66,6 mmol), tetraquistrifenilfosfina Pd(0) (1,1 g, 0,95 mmol) y 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (3,94 g, 18,94 mmol) [preparado de acuerdo con el procedimiento de la Preparación 7]. La mezcla de reacción se calentó a 85ºC en un tubo cerrado herméticamente durante 12 horas y se repartió entre H_2O y $CHCl_3$. El valor del pH de la fase acuosa se ajustó a ~3 con HCl 6 N y se lavó varias veces con $CHCl_3$. Las fracciones orgánicas combinadas se secaron (Na_2SO_4), se concentraron al vacío y se usaron directamente sin purificación adicional (2,84 g, 13,64 mmol, 72%): LC-MS (ES) m/z = 209 $(M+H)^+$.

b) *N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (183 mg, 0,88 mmol), 2-[(2S)-2-amino-3-(3,4-diclorofenil)propil]-1H-isoindolo-1,3(2H)-diona (0,3 g, 0,85 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3,4-difluoro-L-fenilalanina (2,03 g, 6,74 mmol)] y PyBrop (528 mg, 1,13 mmol) en cloroformo (5 ml). Se añadió DIEA (0,77 ml, 4,41 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna

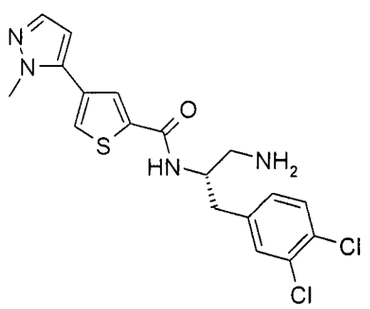
(EtOAc al 25 - 75%/Hex), produciendo el compuesto del título (149 mg, 30%): LC-MS (ES) m/z = 507 $(M+H)^+$

c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (149 mg, 0,265 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (60 µl, 1,91 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

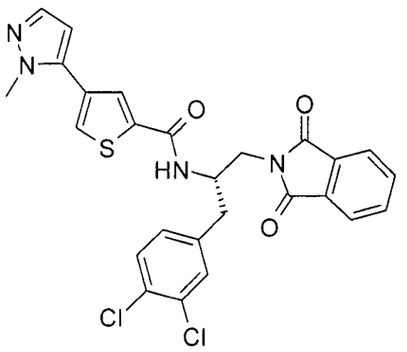
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (71 mg, 0,15 mmol, rendimiento de 57%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,96 (d, *J* = 6,06 Hz, 2 H) 3,00 - 3,06 (m, 2 H) 3,97 (s, 3 H) 4,33 - 4,42 (m, 1 H) 6,48 (d, *J* = 1,77 Hz, 1 H) 7,14 (s, 1 H) 7,30 - 7,42 (m, 2 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,99 (d, *J* = 1,26 Hz, 1 H) 8,22 (s, 3 H) 8,35 (d, *J* = 1,26 Hz, 1 H) 9,09 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 147



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(3,4-diclorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



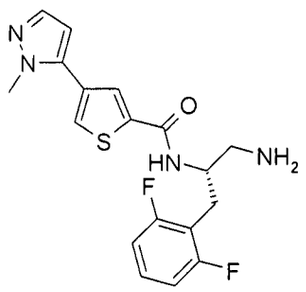
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (160 mg, 0,62 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 146], 2-[(2S)-2-amino-3-(3,4-diclorofenil)propil]-1H-isoindolo-1,3(2H)-diona (0,26 g, 0,67 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3,4-dicloro-*N*-{[(1,1-dimetiletil)oxi]carbonil}-L-fenilalanina (2,03 g, 6,07 mmol)] y PyBrop (376 mg, 0,80 mmol) en cloroformo (4 ml). Se añadió DIEA (0,55 ml, 3,15 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 75%/Hex), produciendo el compuesto del título (149 mg, 30%): LC-MS (ES) m/z = 539 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(3,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(3,4-diclorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (211 mg, 0,34 mmol) en tetrahidrofurano (THF) (4,5 ml) y metanol (0,45 ml). Se añadió hidrazina (75 µl, 2,390 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. Después de que se completara, la mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

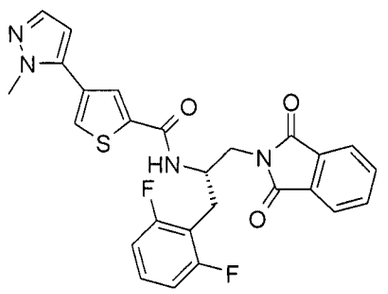
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (83 mg, 0,16 mmol, rendimiento de 48%): LC-MS (ES) m/z = 411 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,95 - 3,07 (m, 4 H) 3,97 (s, 3 H) 4,32 - 4,43 (m, 1 H) 6,48 (d, *J* = 1,77 Hz, 1 H) 7,29 (dd, *J* = 8,21, 1,89 Hz, 1 H) 7,47 (d, *J* = 2,02 Hz, 1 H) 7,54 (d, *J* = 8,08 Hz, 1 H) 7,60 (d, *J* = 1,77 Hz, 1 H) 8,00 (d, *J* = 1,26 Hz, 1 H) 8,22 (s, 3 H) 8,35 (d, *J* = 1,01 Hz, 1 H) 9,11 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 148



Preparación de *N*-{(1*S*)-2-amino-1-[(2,6-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(2,6-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (160 mg, 0,62 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 146], 2-[(2*S*)-2-amino-3-(2,6-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (231 mg, 0,69 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18] y PyBrop (353 mg, 0,75 mmol) en cloroformo (8 ml). Se añadió DIEA (0,64 ml, 3,66 mmol) y la mezcla se agitó durante una

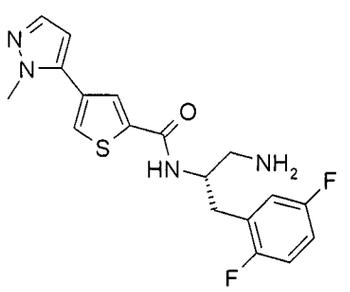
noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 75%/Hex), produciendo el compuesto del título (149 mg, 0,21 mmol, 30%): LC-MS (ES) m/z = 507 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(2,6-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(2,6-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (168 mg, 0,32 mmol) en tetrahidrofurano (THF) (3,6 ml) y metanol (0,4 ml). Se añadió hidrazina (70 µl, 2,23 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

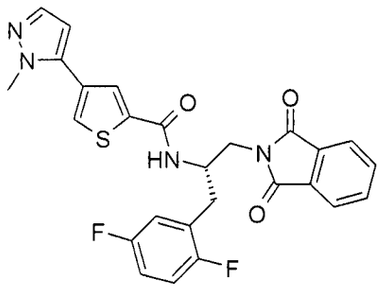
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (101 mg, 0,214 mmol, 68%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,92 - 3,03 (m, 3 H) 3,17 (m, 1 H) 3,97 (s, 3 H) 4,46 (m, 1 H) 6,47 (d, *J* = 1,77 Hz, 1 H) 7,05 (t, *J* = 7,83 Hz, 2 H) 7,27 - 7,38 (m, 1 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,99 (d, *J* = 1,26 Hz, 1 H) 8,23 (d, *J* = 1,26 Hz, 4 H) 8,92 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 149



Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (257 mg, 0,93 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 146], 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (476 mg, 0,81 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (535 mg, 1,14 mmol) en cloroformo (15 ml). Se añadió DIEA (0,808 ml, 4,63 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 75%/Hex), produciendo el compuesto del título (225 mg, 34%): LC-MS (ES) m/z = 507 $(M+H)^+$

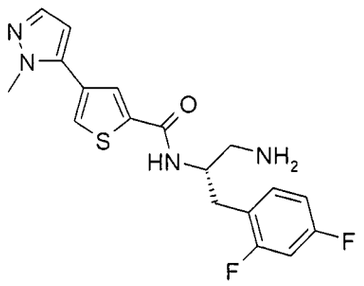
b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (225 mg, 0,31 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (0,8 ml). Se añadió hidrazina (60 µl, 1,91 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH). El compuesto se purificó adicionalmente sobre HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%), produciendo la sal TFA que se neutralizó sobre sílice (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título

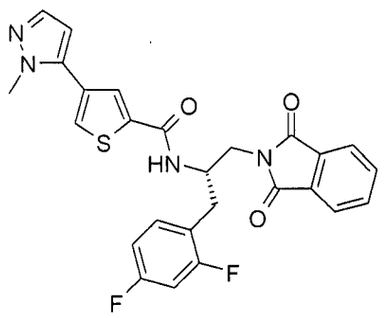
(90,5 mg, 0,19 mmol, 63%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,95 - 3,01 (m, 2 H) 3,03 - 3,10 (m, 2 H) 3,92 - 3,98 (m, 3 H) 4,41 - 4,51 (m, 1 H) 6,47 (d, *J* = 1,77 Hz, 1 H) 7,05 - 7,13 (m, 1 H) 7,20 (td, *J* = 9,09, 4,55 Hz, 1 H) 7,27 (ddd, *J* = 9,09, 5,81, 3,28 Hz, 1 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,99 (d, *J* = 1,52 Hz, 1 H) 8,18 (s, 3 H) 8,29 (d, *J* = 1,26 Hz, 1 H) 9,03 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 150



Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(2,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadió ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (222 mg, 0,80 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 146], 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (331 mg, 0,78 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (1,0 g, 4,97 mmol)] y PyBrop (448 mg, 0,96 mmol) en cloroformo (10 ml). Se añadió DIEA (700 µl, 4,01 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla de

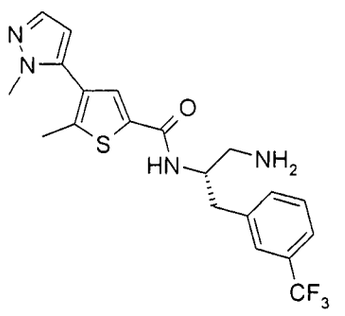
reacción se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 75%/Hex), produciendo el compuesto del título (249 mg, 0,36 mmol, 46%): LC-MS (ES) m/z = 507 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(2,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (249 mg, 0,36 mmol) en tetrahidrofurano (THF) (5 ml) y metanol (1 ml). Se añadió hidrazina (80 µl, 2,55 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH). El compuesto se purificó adicionalmente sobre HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%), produciendo la sal TFA que se neutralizó sobre sílice (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

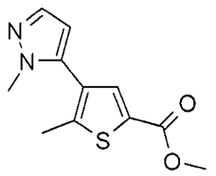
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (81 mg, 0,18 mmol, 50%): LC-MS (ES) m/z = 377 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,88 - 2,98 (m, 2 H) 2,98 - 3,09 (m, 2 H) 3,93 - 3,98 (m, 3 H) 4,38 - 4,47 (m, 1 H) 6,47 (d, *J* = 1,77 Hz, 1 H) 7,00 (td, *J* = 8,46, 2,27 Hz, 1 H) 7,19 (td, *J* = 9,85, 2,53 Hz, 1 H) 7,38 - 7,45 (m, 1 H) 7,47 (d, *J* = 1,77 Hz, 1 H) 7,99 (d, *J* = 1,26 Hz, 1 H) 8,18 (s a, 3 H) 8,27 (d, *J* = 1,26 Hz, 1 H) 8,99 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 151



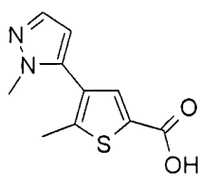
Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



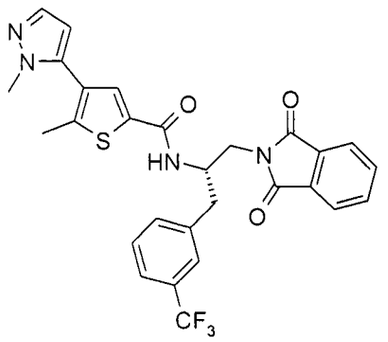
A un matraz cerrado herméticamente de 125 ml se le añadieron 4-bromo-5-metil-2-tiofenocarboxilato de metilo (1,56 g, 6,64 mmol) [preparado de acuerdo con el procedimiento de la Preparación 10], 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,67 g, 8,03 mmol) [preparada de acuerdo con el procedimiento de la Preparación 7], K_2CO_3 (2,76 g, 19,97 mmol) y $Pd(PtBu_3)_2$ (170 mg, 0,33 mmol) en 1,4-dioxano (27 ml) y agua (7 ml). La mezcla de reacción se calentó a 85°C en un tubo cerrado herméticamente durante 3 horas, se enfrió a temperatura ambiente y se repartió entre H_2O y $CHCl_3$. La fracción orgánica se secó (Na_2SO_4), se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 0-15%/Hexano). (385 mg, 1,4 mmol, 30%): LC-MS (ES) m/z = 237 $(M+H)^+$.

b) ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (1,34 g, 5,67 mmol) en tetrahidrofurano (THF) (31 ml). Se añadió NaOH 6 N (31 ml, 186 mmol) y la mezcla de reacción se agitó a 70°C durante una noche. La mezcla de reacción se neutralizó mediante la adición lenta de HCl 6 N y se repartió entre $CHCl_3$ y H_2O. Las capas se separaron, la capa orgánica se secó con Na_2SO_4 y el disolvente se retiró. El sólido resultante se usó sin purificación adicional (0,71 g, 2,81 mmol, 96%): LC-MS (ES) m/z = 223 $(M+H)^+$.

c) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



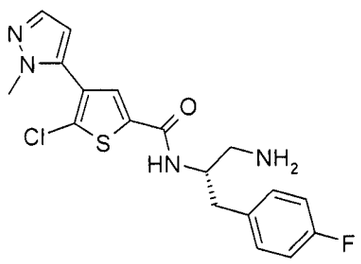
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (201 mg, 0,91 mmol), 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (301 mg, 0,87 mmol) [preparada de acuerdo con la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 14,95 mmol)] y PyBrop (519 mg, 1,11 mmol) en cloroformo (9 ml). Se añadió DIEA (790 µl, 4,52 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (247 mg, 45%): LC-MS (ES) m/z = 553 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (374 mg, 0,64 mmol) en tetrahidrofurano (THF) (6 ml) y metanol (600 µl). Se añadió hidrazina (125 µl, 3,98 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

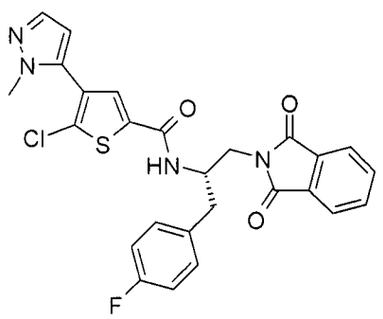
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (135 mg, 0,27 mmol, rendimiento de 42%): LC-MS (ES) m/z = 423 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,37 (s, 3 H) 2,95 - 3,11 (m, 4 H) 3,78 (s, 3 H) 4,32 - 4,42 (m, 1 H) 6,34 (d, *J* = 1,77 Hz, 1 H) 7,48 - 7,56 (m, 3 H) 7,58 - 7,61 (m, 1 H) 7,67 (s, 1 H) 8,04 (s, 1 H) 8,21 (s, 3 H) 8,98 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 152



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (201 mg, 0,91 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 95], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (301 mg, 0,87 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y

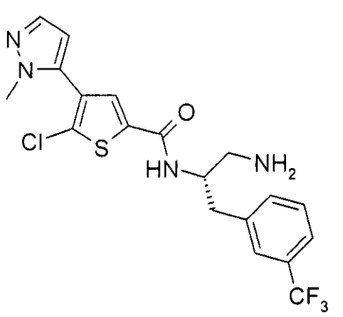
PyBrop (519 mg, 1,11 mmol) en cloroformo (9 ml). Se añadió DIEA (790 µl, 4,52 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (186 mg, 32%): LC-MS (ES) m/z = 553 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (185 mg, 0,34 mmol) en tetrahidrofurano (THF) (10 ml) y metanol (1 ml). Se añadió hidrazina (63 µl, 2,0 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

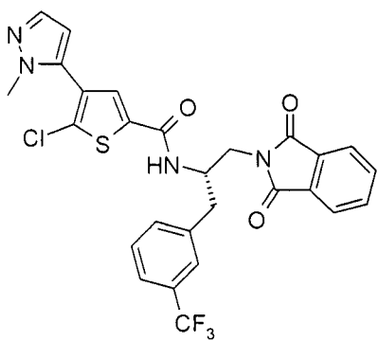
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (101 mg, 0,24 mmol, 72%): LC-MS (ES) m/z = 393 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,90 - 3,1 (m, 4 H) 3,85 (s, 3 H) 4,33 (s, 1 H) 6,48 (d, *J* = 1,77 Hz, 1 H) 7,10 (t, *J* = 8,84 Hz, 2 H) 7,32 (dd, *J* = 8,46, 5,68 Hz, 2 H) 7,55 (d, *J* = 2,02 Hz, 1 H) 8,19 (s, 3 H) 8,23 - 8,28 (m, 1 H) 9,25 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 153



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



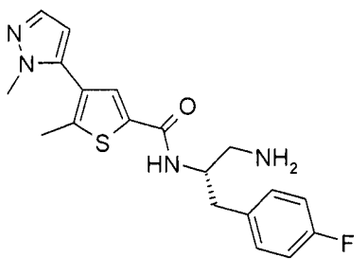
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (226 mg, 0,93 mmol) [preparada de acuerdo con el procedimiento del Ejemplo 95], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (519 mg, 1,349 mmol) [preparada de acuerdo con la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (515 mg, 1,1 mmol) en cloroformo (10 ml). Se añadió DIEA (820 µl, 4,70 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (379 mg, 69%): LC-MS (ES) m/z = 573 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (378 mg, 0,64 mmol) en tetrahidrofurano (THF) (10 ml) y metanol (1 ml). Se añadió hidrazina (122 µl, 3,89 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

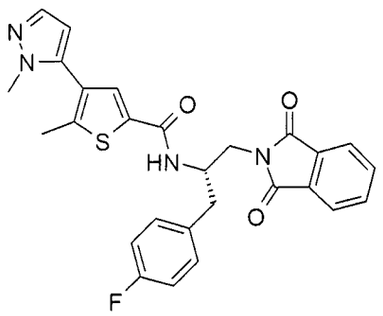
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (222 mg, 0,41 mmol, 64%): LC-MS (ES) m/z = 443 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 3,05 (d, *J* = 6,82 Hz, 4 H) 3,84 (s, 3 H) 4,37 (d, *J* = 5,05 Hz, 1 H) 6,46 (d, *J* = 1,77 Hz, 1 H) 7,49 - 7,57 (m, 3 H) 7,58 - 7,61 (m, 1 H) 7,67 (s, 1 H) 8,20 (s, 3 H) 8,24 (s, 1 H) 9,31 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 154



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (200 mg, 0,90 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 151], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (288 mg, 0,86 mmol) [preparada de acuerdo con la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-

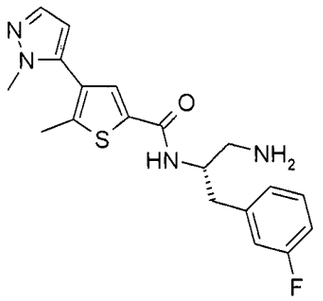
dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (512 mg, 1,09 mmol) en cloroformo (9 ml). Se añadió DIEA (790 µl, 4,52 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (162 mg, 32%): LC-MS (ES) m/z = 503 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (162 mg, 0,29 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (300 µl). Se añadió hidrazina (58 µl, 1,85 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH): El compuesto se purificó adicionalmente sobre HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%), produciendo la sal TFA que se neutralizó sobre sílice (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

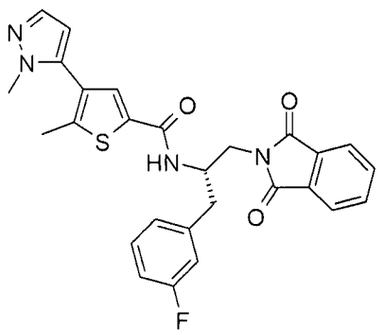
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (222 mg, 0,41 mmol, 64%): LC-MS (ES) m/z = 373 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,38 (s, 3 H) 2,89 - 3,02 (m, 4 H) 3,79 (s, 3 H) 4,26 - 4,48 (m, 1 H) 6,36 (d, *J* = 1,77 Hz, 1 H) 7,10 (t, *J* = 8,72 Hz, 2 H) 7,26 - 7,35 (m, 2 H) 7,52 (d, *J* = 1,77 Hz, 1 H) 8,02 (s, 1 H) 8,17 (s, 3 H) 8,88 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 155



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



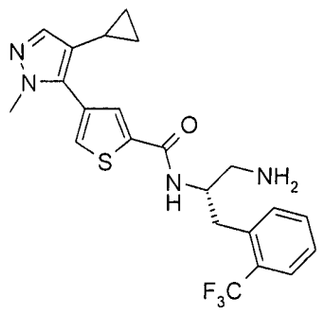
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (200 mg, 0,90 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 151], 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (291 mg, 0,87 mmol) [preparada de acuerdo con el procedimiento de la preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,8 mmol)] y PyBrop (512 mg, 1,09 mmol) en cloroformo (9 ml). Se añadió DIEA (790 µl, 4,52 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (250 mg, 50%): LC-MS (ES) m/z = 503 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (250 mg, 0,45 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (400 µl). Se añadió hidrazina (66 µl, 2,10 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH). El compuesto se purificó adicionalmente sobre HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%), produciendo la sal TFA que se neutralizó sobre sílice (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

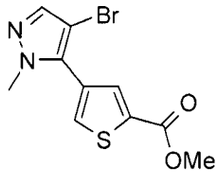
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (142 mg, 0,31 mmol, 70%): LC-MS (ES) m/z = 373 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,38 (s, 3 H) 2,92 - 3,04 (m, 4 H) 3,79 (s, 3 H) 4,30 -4,43 (m, 1 H) 6,36 (d, *J* = 1,77 Hz, 1 H) 7,02 (td, *J* = 8,53, 2,15 Hz, 1 H) 7,13 (t, *J* = 7,83 Hz, 2 H) 7,26 - 7,35 (m, 1 H) 7,52 (d, *J* = 2,02 Hz, 1 H) 8,04 (s, 1 H) 8,19 (s, 3 H) 8,93 (d, *J* = 8,34 Hz, 1 H).

Ejemplo 156



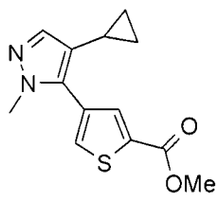
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



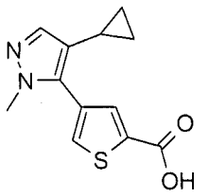
Se añadió en porciones NBS (747 mg, 4,20 mmol) a un tubo reactor cerrado herméticamente de 50 ml que contenía 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (860 mg, 3,48 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 37] en tetrahidrofurano (THF) (17 ml) a temperatura ambiente. La mezcla se calentó a 70°C durante 1,5 horas, se enfrió a temperatura ambiente y se repartió entre $CHCl_3$ y H_2O. La capa orgánica se secó con Na_2SO_4, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 20 - 40%/hexanos), produciendo el compuesto del título (867 mg, 83%): LC-MS (ES) m/z = 303 $(M+H)^+$.

b) 4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



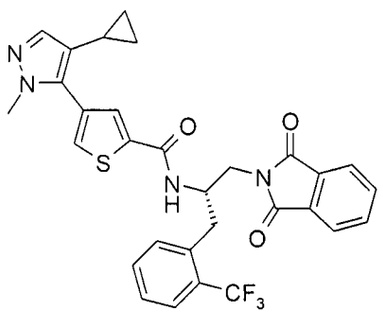
A un tubo reactor cerrado herméticamente de 20 ml se le añadieron 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (505 mg, 1,68 mmol), ácido ciclopropilborónico (447 mg, 5,20 mmol), carbonato de cesio (1,90 g, 5,84 mmol) y aducto de $PdCl_2$(dppf)-CH_2Cl_2 (43,6 mg, 0,05 mmol) en tetrahidrofurano (THF) (8,5 ml). La reacción se calentó a 70°C durante 1,5 horas, se enfrió y se repartió entre $CHCl_3$ y H_2O. La capa orgánica se secó con Na_2SO_4, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 20 - 40%/Hexano), produciendo el compuesto del título (0,42 g, 1,60 mmol, 95%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) ácido 4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 4-(4-ciclopropil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (0,42 g, 1,60 mmol) en tetrahidrofurano (THF) (8 ml). Se añadió lentamente NaOH 6 N (8 ml, 48,0 mmol) y la reacción se agitó a 70°C durante una noche. La reacción se enfrió y se repartió entre $CHCl_3$ y H_2O. El valor del pH de la capa acuosa se ajustó a ~3 mediante la adición de HCl 6 N. Las capas se separaron, la capa orgánica se secó con Na_2SO_4 y el disolvente se retiró produciendo el compuesto del título (0,42 g, 1,60 mmol, 95%) que se usó sin purificación adicional: LC-MS (ES) m/z = 249 $(M+H)^+$.

d) 4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



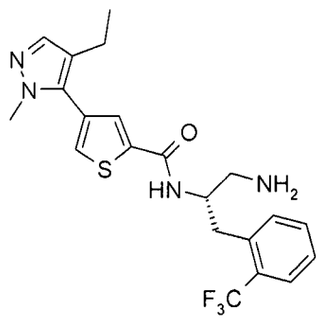
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-ciclopropil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (105 mg, 0,42 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (152 mg, 0,39 mmol) [preparada de acuerdo con la Preparación 6] y PyBrop (246 mg, 0,52 mmol) en cloroformo (6 ml). Se añadió DIEA (370 µl, 2,19 mmol) y la mezcla se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (171 mg, 66%): LC-MS (ES) m/z = 579 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-ciclopropil-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (102 mg, 0,18 mmol) en tetrahidrofurano (THF) (5 ml) y metanol (2 ml). Se añadió hidrazina (40 µl, 1,27 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

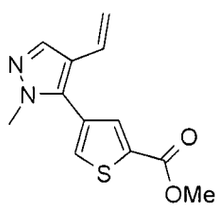
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (65 mg, 0,12 mmol, rendimiento de 66%): LC-MS (ES) m/z = 449 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 0,45 - 0,54 (m, 2 H) 0,76 - 0,83 (m, 2 H) 1,62 - 1,71 (m, 1 H) 3,03 - 3,21 (m, 4 H) 3,82 (s, 3 H) 4,46 - 4,56 (m, 1 H) 7,21 (s, 1 H) 7,42 (t, *J* = 7,45 Hz, 1 H) 7,53 (t, *J* = 7,45 Hz, 1 H) 7,66 (dd, *J* = 19,96, 7,58 Hz, 2 H) 7,95 (d, *J* = 1,26 Hz, 1 H) 8,18 (s, 3 H) 8,24 (d, *J* = 1,26 Hz, 1 H) 9,11 (d, *J* = 9,09 Hz, 1 H).

Ejemplo 157



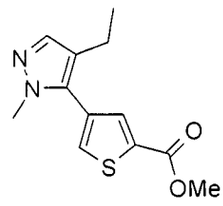
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(4-etenil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



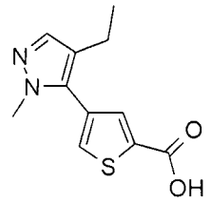
A un tubo reactor cerrado herméticamente de 5 ml se le añadieron 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (473 mg, 1,57 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 156], piridina - trietenilboroxina (1:1) (666 mg, 2,77 mmol), $Pd(PtBu_3)_2$ (16,8 mg, 0,03 mmol) y Cs_2CO_3 (1,72 g, 5,28 mmol) en 1,4-dioxano (6,3 ml) y agua (1,6 ml). La reacción se calentó a 70°C durante 2 horas y se repartió entre $CHCl_3$ (75 ml)/H_2O (75 ml). La capa orgánica se secó con Na_2SO_4, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25-70%/Hexano), produciendo el producto deseado: LC-MS (ES) m/z = 249 $(M+H)^+$.

b) 4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



A un matraz de fondo redondo de 100 ml se le añadieron 4-(4-etenil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo y Pd al 10%/C en acetato de etilo (15 ml). La mezcla se evacuó ligeramente, se recargó con un globo de H_2 y se agitó vigorosamente en una atmósfera de H_2 durante 1 hora. La reacción se filtró a través de un filtro de membrana de PTFE de 0,2 µm y se usó sin purificación adicional (153 mg, 0,60 mmol, 87%): LC-MS (ES) m/z = 251 $(M+H)^+$.

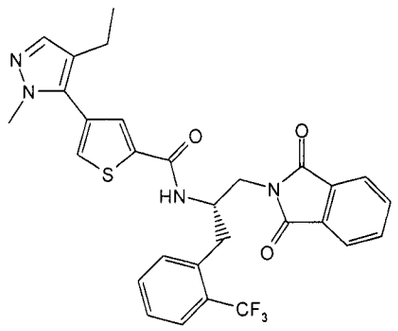
c) ácido 4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (192 mg, 0,77 mmol) en tetrahidrofurano (THF) (4 ml). Se añadió lentamente NaOH 6 N (4 ml, 24,0 mmol) y la reacción se agitó a 70°C durante una noche. La reacción se enfrió a temperatura ambiente, se repartió entre $CHCl_3$ y H_2O y el valor del pH de la capa acuosa se ajustó a pH 3 mediante la adición de HCl 6 N. Las capas se separaron, la capa orgánica se secó

con Na_2SO_4 y el disolvente se retiró produciendo el compuesto del título (181 mg, cuant.) que se usó sin purificación adicional: LC-MS (ES) m/z = 237 $(M+H)^+$.

d) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (106 mg, 0,45 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (164 mg, 0,43 mmol) [preparada de acuerdo con la Preparación 6] y PyBrop (254 mg, 0,54 mmol) en cloroformo (6 ml). Se añadió DIEA (400 µl, 2,29 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (182 mg, 0,32 mmol, 71%): LC-MS (ES) m/z = 567 $(M+H)^+$.

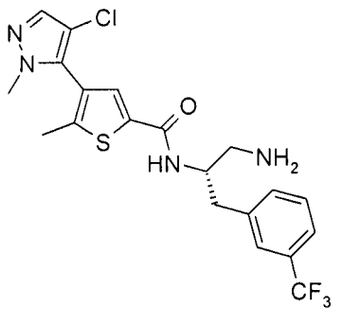
e) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (101 mg, 0,18 mmol) en tetrahidrofurano (THF) (5 ml) y metanol (2 ml). Se añadió hidrazina (40 µl, 1,27 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (65 mg, 0,12 mmol, 68%): LC-MS (ES) m/z = 437 $(M+H)^+$, ^1H RMN (400 MHz,

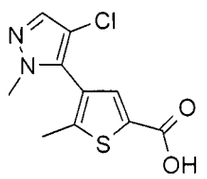
DMSO-d_6) ppm 1,10 (t, J = 7,45 Hz, 3 H) 2,44 (c, J = 7,41 Hz, 2 H) 2,94 - 3,17 (m, 4 H) 3,80 (s, 3 H) 4,41 - 4,57 (m, 1 H) 7,37 - 7,45 (m, 2 H) 7,53 (t, J = 7,45 Hz, 1 H) 7,66 (dd, J = 19,96, 7,58 Hz, 2 H) 7,88 (d, J = 1,01 Hz, 1 H) 8,16 (s, 4 H) 9,10 (d, J = 8,84 Hz, 1 H).

Ejemplo 158



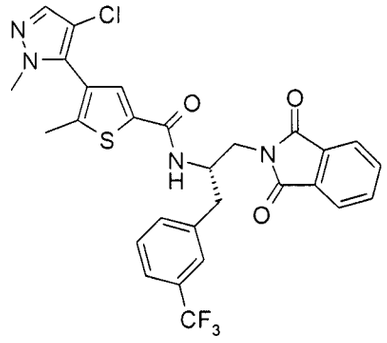
Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) ácido 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxílico



Se añadió en porciones NCS (1,355 g, 10,15 mmol) a un tubo reactor cerrado herméticamente de 150 ml que contenía 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,0 g, 8,46 mmol) [preparado de acuerdo con el procedimiento de la Preparación 10] en tetrahidrofurano (THF) (40 ml) a temperatura ambiente. La mezcla se calentó a 70°C durante 2 h. Se añadió NaOH 6 N (28 ml, 168 mmol) y la mezcla se agitó a 70°C durante 2 h más. La mezcla se enfrió a temperatura ambiente y se repartió entre $CHCl_3$ y H_2O. El valor del pH de la capa acuosa se ajustó a ~3 mediante la adición de HCl 6 N. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron con Na_2SO_4 y se concentraron, produciendo el compuesto del título (2,36 g, 9,19 mmol, cuant.): LC-MS (ES) m/z = 257 $(M+H)^+$.

b) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida



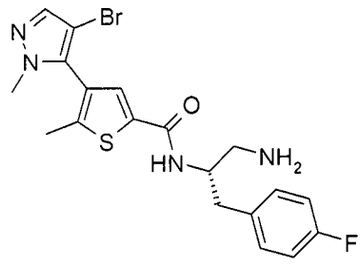
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (181 mg, 0,70 mmol), 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (250 mg, 0,65 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (399 mg, 0,85 mmol) en cloroformo (8 ml). Se añadió DIEA (620 µl, 3,55 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (319 mg, 0,50 mmol, 71%): LC-MS (ES) m/z = 587 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida (319 mg, 0,50 mmol) en tetrahidrofurano (THF) (4,9 ml) y metanol (0,5 ml). Se añadió hidrazina (119 µl, 3,79 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

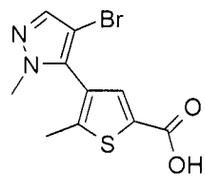
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (204 mg, 0,39 mmol, 79%): LC-MS (ES) m/z = 457 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,33 (s, 3 H) 2,95 - 3,10 (m, 4 H) 3,71 (s, 3 H) 4,31 - 4,41 (m, 1 H) 7,49 - 7,61 (m, 3 H) 7,66 (s, 1 H) 7,69 (s, 1 H) 7,94 (s, 1 H) 8,16 (s, 3 H) 8,90 (s, 1 H).

Ejemplo 159



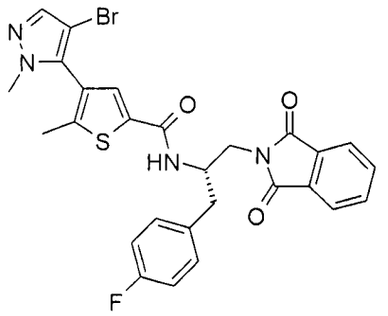
Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) ácido 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxílico



Se añadió en porciones NBS (1,84 g, 10,33 mmol) a un tubo reactor cerrado herméticamente de 150 ml que contenía 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2 g, 8,46 mmol) [preparado de acuerdo con el procedimiento de la Preparación 10] en tetrahidrofurano (THF) (40 ml) a temperatura ambiente. La mezcla se calentó a 70°C durante 1 h. Después, se añadió NaOH 6 N (28 ml, 168 mmol) y la mezcla se agitó a 70°C durante 2 h. La mezcla se repartió entre $CHCl_3$ y H_2O y la capa acuosa se hizo básica con HCl 6 N. La fase acuosa se lavó varias veces con $CHCl_3$ y las fracciones orgánicas se combinaron, se secaron sobre Na_2SO_4 y se concentraron, produciendo el compuesto del título (2,68 g, 8,9 mmol, cuant.): LC-MS (ES) m/z = 302 $(M+H)^+$.

b) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadió ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (256 mg, 0,85 mmol), 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (1272 mg, 3,80 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (485 mg, 1,03 mmol) en cloroformo (8,5 ml). Se añadió DIEA (750 µl, 4,29 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (319 mg, 0,50 mmol, 71%): LC-MS (ES) m/z = 583 $(M+H)^+$.

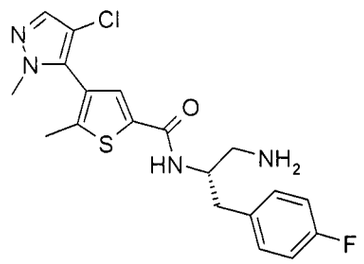
c) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida (133 mg, 0,21 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1 ml). Se añadió hidrazina (50 µl, 1,59 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título

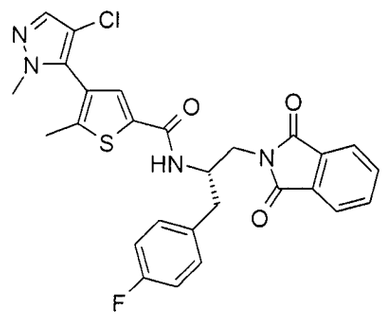
(90 mg, 0,17 mmol, 83%): LC-MS (ES) m/z = 453 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,33 (s, 3 H) 2,82 - 3,08 (m, 4 H) 3,72 (s, 3 H) 4,24 - 4,39 (m, 1 H) 7,11 (t, J = 8,84 Hz, 2 H) 7,26 - 7,35 (m, 2 H) 7,69 (s, 1 H) 7,89 (s, 1 H) 8,03 - 8,25 (m, 3 H) 8,73 - 8,90 (m, 1 H).

Ejemplo 160



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (276 mg, 1,08 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 158], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (317 mg, 0,95 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (612 mg, 1,31 mmol) en cloroformo (14 ml). Se añadió DIEA (940 µl, 5,38 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 -

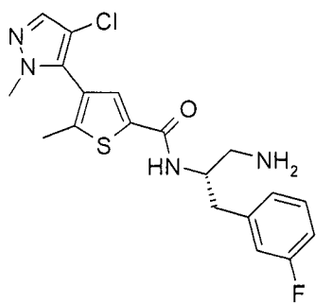
70%/Hex), produciendo el compuesto del título (319 mg, 0,50 mmol, 71%): LC-MS (ES) m/z = 537 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida (145 mg, 0,25 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (60 µl, 1,91 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

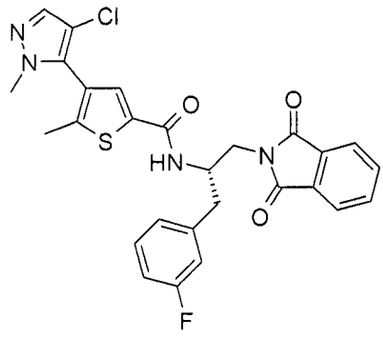
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (88 mg, 0,19 mmol, 77%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,34 (s, 3 H) 2,81 - 3,10 (m, 4 H) 3,72 (s, 3 H) 4,25 - 4,40 (m, 1 H) 7,10 (t, *J* = 8,84 Hz, 2 H) 7,31 (dd, *J* = 8,21, 5,68 Hz, 2 H) 7,69 (s, 1 H) 7,94 (s, 1 H) 8,15 (s, 3 H) 8,85 (s, 1 H).

Ejemplo 161



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (187 mg, 0,73 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 158], 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (233 mg, 0,70 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,8 mmol)] y PyBrop (412 mg, 0,88 mmol) en cloroformo (9 ml). Se añadió DIEA (640 µl, 3,66 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (180 mg, 0,30 mmol, 42%): LC-MS (ES) m/z = 537 $(M+H)^+$.

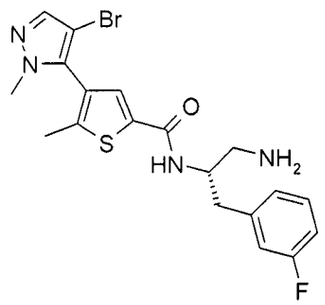
b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida (186 mg, 0,31 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (76 µl, 2,42 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (108 mg, 0,231, 74%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-

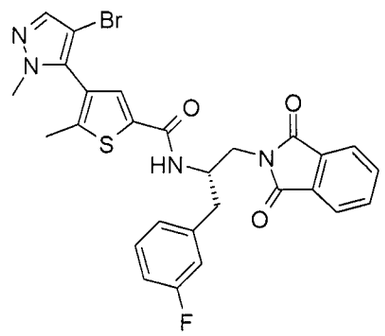
d_6) ppm 2,34 (s, 3 H) 2,91 - 3,03 (m, 4 H) 3,71 (s, 3 H) 4,31 - 4,41 (m, 1 H) 7,02 (td, *J* = 8,59, 2,02 Hz, 1 H) 7,13 (t, *J* = 7,07 Hz, 2 H) 7,26 - 7,36 (m, 1 H) 7,69 (s, 1 H) 7,95 (s, 1 H) 8,15 (s, 3 H) 8,88 (d, *J* = 6,32 Hz, 1 H).

Ejemplo 162



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (191 mg, 0,63 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 159], 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (209 mg, 0,62 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,8 mmol)] y PyBrop (359 mg, 0,77 mmol) en cloroformo (7 ml). Se añadió DIEA (560 µl, 3,21 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se

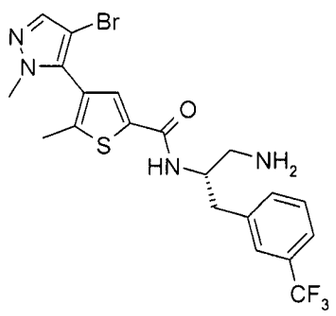
absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (171 mg, 0,29 mmol, 46%): LC-MS (ES) m/z = 583 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida (171 mg, 0,29 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1 ml). Se añadió hidrazina (66 µl, 2,10 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

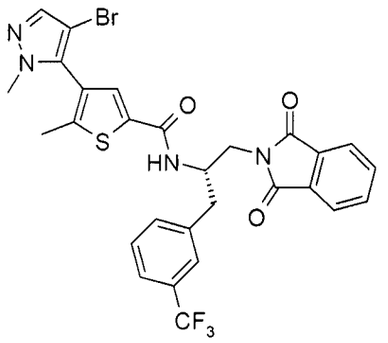
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (123 mg, 0,26 mmol, 88%): LC-MS (ES) m/z = 453 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,33 (s, 3 H) 2,91 - 3,03 (m, 4 H) 3,72 (s, 3 H) 4,31 - 4,41 (m, 1 H) 7,02 (td, *J* = 8,46, 2,02 Hz, 1 H) 7,12 (d, *J* = 7,33 Hz, 2 H) 7,27 - 7,35 (m, 1 H) 7,64 - 7,71 (m, 1 H) 7,92 (s, 1 H) 8,14 (s, 3 H) 8,79 - 8,93 (m, 1 H).

Ejemplo 163



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida



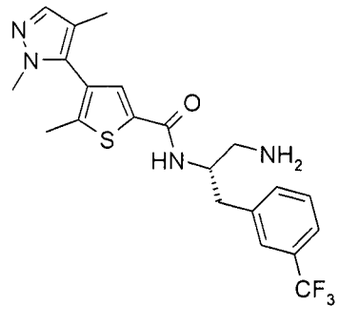
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (180 mg, 0,60 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 159], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (203 mg, 0,58 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (340 mg, 0,72 mmol) en cloroformo (6 ml). Se añadió DIEA (530 µl, 3,03 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (259 mg, 0,41 mmol, 69%): LC-MS (ES) m/z = 633 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-bromo-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida (259 mg, 0,41 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1 ml). Se añadió hidrazina (90 µl, 2,87 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

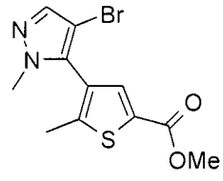
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (172 mg, 0,33 mmol, 80%): LC-MS (ES) m/z = 503 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,32 (s, 3 H) 3,03 (d, *J* = 6,06 Hz, 4 H) 3,71 (d, *J* = 5,81 Hz, 3 H) 4,31 - 4,41 (m, 1 H) 7,49 - 7,56 (m, 2 H) 7,60 (d, *J* = 6,82 Hz, 1 H) 7,64 - 7,71 (m, 2 H) 7,93 (d, *J* = 12,88 Hz, 1 H) 8,18 (s, 3 H) 8,88 - 8,99 (m, 1 H).

Ejemplo 164



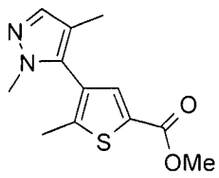
Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo



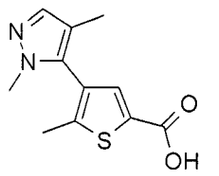
Se añadió en porciones NBS (2,03 g, 11,41 mmol) a un tubo reactor cerrado herméticamente de 75 ml que contenía 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,1 g, 8,89 mmol) [preparado de acuerdo con el procedimiento de la Preparación 10] en tetrahidrofurano (THF) (40 ml) a temperatura ambiente. La mezcla se calentó a 70ºC durante 1 hora. La mezcla de reacción se repartió entre $CHCl_3$ y H_2O, la capa orgánica se secó con Na_2SO_4 y la mezcla de reacción se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 15 - 40%/Hex), produciendo el compuesto del título (2,57 g, 8,15 mmol, 92%): LC-MS (ES) m/z = 316 $(M+H)^+$.

b) 4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo



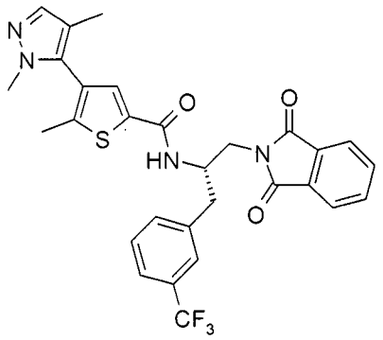
A un matraz reactor cerrado herméticamente de 350 ml se le añadieron 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (2,57 g, 8,15 mmol), trimetilboroxina (2,27 ml, 16,31 mmol), K_2CO_3 (3,47 g, 25,1 mmol) y $Pd(dppf)Cl_2$ (426 mg, 0,83 mmol) en N,N-dimetilformamida (DMF) (41 ml). La reacción se calentó a 110ºC durante 1 hora. La mezcla se repartió entre $CHCl_3/H_2O$ y la capa orgánica se separó y se secó con Na_2SO_4. El material resultante se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 0-15%/Hexano), produciendo el compuesto del título (1,3 g, 4,76 mmol, 58%): LC-MS (ES) m/z = 251 $(M+H)^+$.

c) ácido 4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxilato de metilo (1,31 g, 5,23 mmol) en tetrahidrofurano (THF) (25 ml). Se añadió lentamente NaOH 6 N (30 ml, 180 mmol) y la reacción se agitó a 70ºC durante una noche. La reacción se enfrió a temperatura ambiente, se repartió entre $CHCl_3$ y H_2O y el valor del pH de la capa acuosa se ajustó a pH 3 mediante la adición de HCl 6 N. Las capas se separaron, la capa orgánica se secó con Na_2SO_4 y el disolvente se retiró produciendo el compuesto del título (1,3 g, 5,5 mmol, cuant.) que se usó sin purificación adicional: LC-MS (ES) m/z = 237 $(M+H)^+$.

d) 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (170 mg, 0,68 mmol), 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (256 mg, 0,67 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (387 mg, 0,83 mmol) en cloroformo (7 ml). Se añadió DIEA (600 µl, 3,44 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (311 mg, 0,55 mmol, 80%): LC-MS (ES) m/z = 567 $(M+H)^+$.

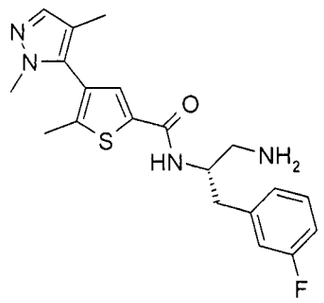
e) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-tiofenocarboxamida (311 mg, 0,55 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1,4 ml). Se añadió hidrazina (122 µl, 3,89 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (234 mg, 0,44 mmol, 79%): LC-MS (ES) m/z = 437 $(M+H)^+$, ^{1}H RMN (400 MHz,

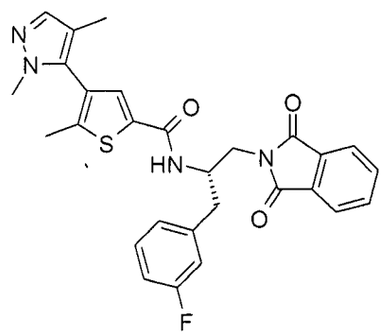
DMSO-d_6) ppm 1,87 (s, 3 H) 2,26 (s, 3 H) 3,03 (d, *J* = 6,82 Hz, 4 H) 3,62 (s, 3 H) 4,31 - 4,41 (m, 1 H) 7,38 (s, 1 H) 7,49 - 7,56 (m, 2 H) 7,58 - 7,61 (m, 1 H) 7,65 (s, 1 H) 7,87 (s, 1 H) 8,20 (s, 3 H) 8,89 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 165



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (207 mg, 0,83 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 164], 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (279 mg, 0,83 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,8 mmol)] y PyBrop (469 mg, 1,00 mmol) en cloroformo (8 ml). Se añadió DIEA (730 µl, 4,18 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se

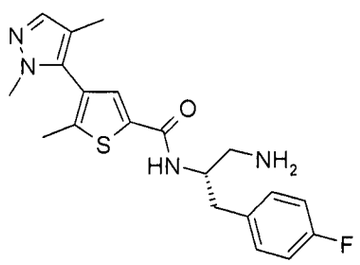
absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (209 mg, 0,36 mmol, 43%): LC-MS (ES) m/z = 517 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(1,4-dimetil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida (201 mg, 0,39 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (86 µl, 2,74 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

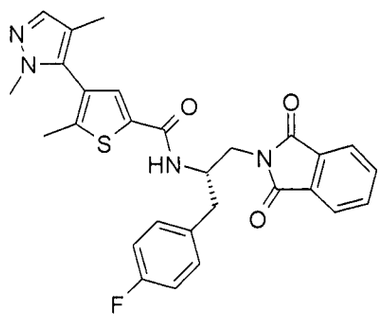
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (163 mg, 0,34 mmol, 87%): LC-MS (ES) m/z = 387 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 1,88 (s, 3 H) 2,27 (s, 3 H) 2,87 - 3,09 (m, 4 H) 3,17 3,63 (s, 3 H) 4,28 - 4,45 (m, 1 H) 6,97 - 7,06 (m, 1 H) 7,13 (t, *J* = 7,20 Hz, 2 H) 7,27 - 7,35 (m, 1 H) 7,38 (s, 1 H) 7,89 (s, 1 H) 8,20 (s, 3 H) 8,88 (d, *J* = 7,58 Hz, 1 H).

Ejemplo 166



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (253 mg, 1,02 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 164], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (335 mg, 1,00 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (574 mg, 1,23 mmol) en cloroformo (10 ml). Se añadió DIEA (930 µl, 5,32 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (132 mg, 0,25 mmol, 24%): LC-MS (ES) m/z = 517 $(M+H)^+$.

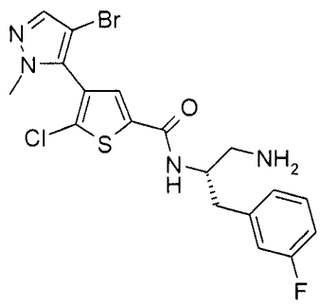
b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(1,4-dimetil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-tiofenocarboxamida (132 mg, 0,26 mmol) en tetrahidrofurano (THF) (2 ml) y metanol (1 ml). Se añadió hidrazina (57 µl, 1,82 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (95:5:0,5 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (104 mg, 0,22 mmol, 84%): LC-MS (ES) m/z = 387 $(M+H)^+$, ^{1}H RMN (400 MHz,

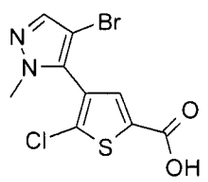
DMSO-d_6) ppm 1,88 (s, 3 H) 2,27 (s, 3 H) 2,84 - 3,11 (m, 4 H) 3,63 (s, 3 H) 4,24 - 4,39 (m, 1 H) 7,10 (t, J = 8,72 Hz, 2 H) 7,31 (dd, J = 8,21, 5,68 Hz, 2 H) 7,38 (s, 1 H) 7,87 (s, 1 H) 8,18 (s, 3 H) 8,83 (s, 1 H).

Ejemplo 167



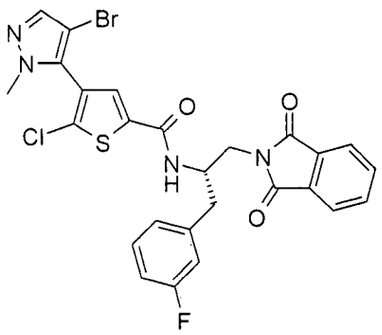
Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

a) ácido 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxílico



Se añadió en porciones NBS (1,243 g, 6,98 mmol) a un tubo reactor cerrado herméticamente de 150 ml que contenía 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (1,47 g, 5,73 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 151] en tetrahidrofurano (THF) (40 ml) a temperatura ambiente. La mezcla se calentó a 70ºC durante 1 h. Después, se añadió NaOH 6 N (20 ml, 120 mmol) y la mezcla se agitó a 70ºC durante 2 h más. La mezcla se repartió entre $CHCl_3$ y H_2O y la capa orgánica se secó con Na_2SO_4 y se concentró, produciendo el compuesto del título que se usó sin purificación adicional (385 mg, 1,4 mmol, 30%): LC-MS (ES) m/z = 302 $(M+H)^+$.

b) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxílico (204 mg, 0,60 mmol), 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (215 mg, 0,64 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,7 mmol)] y PyBrop (380 mg, 0,81 mmol) en cloroformo (6 ml). Se añadió DIEA (570 µl, 3,26 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (247 mg, 45%): LC-MS (ES) m/z = 603 $(M+H)^+$.

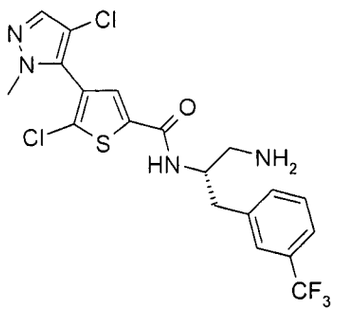
c) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (133 mg, 0,22 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1,2 ml). Se añadió hidrazina (50 µl, 1,59 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (145 mg, 0,30 mmol, rendimiento de 66%): LC-MS (ES) m/z = 473 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,91 - 3,03 (m, 4 H) 3,77 (s, 3 H) 4,30 - 4,41 (m, 1 H)

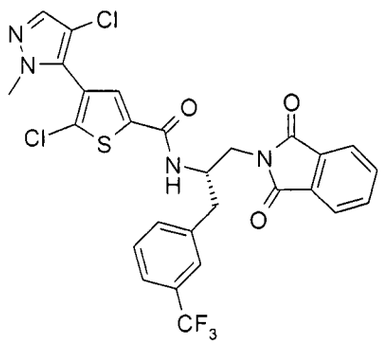
7,04 (td, *J* = 8,53, 2,15 Hz, 1 H) 7,12 (d, *J* = 7,07 Hz, 2 H) 7,28 - 7,36 (m, 1 H) 7,74 (s, 1 H) 8,02 - 8,14 (m, 4 H) 9,06 (s, 1 H).

Ejemplo 168



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (264 mg, 0,95 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 96], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (306 mg, 0,80 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (450 mg, 0,96 mmol) en cloroformo (7 ml). Se añadió DIEA (660 µl, 3,78 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La

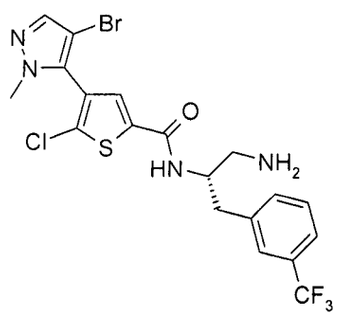
mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (303 mg, 0,44 mmol, 56%): LC-MS (ES) m/z = 607 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (303 mg, 0,50 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1,5 ml). Se añadió hidrazina (120 µl, 3,82 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

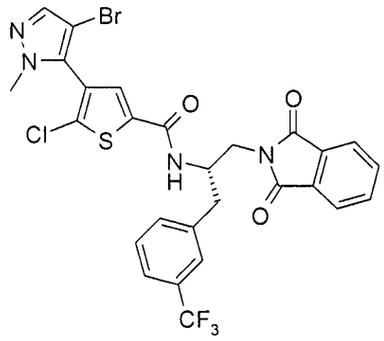
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (177 mg, 0,31 mmol, rendimiento de 61%): LC-MS (ES) m/z = 479 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,97 - 3,08 (m, 4 H) 3,76 (s, 3 H) 4,28 - 4,44 (m, 1 H) 7,50 - 7,61 (m, 3 H) 7,66 (s, 1 H) 7,71 - 7,75 (m, 1 H) 8,10 (s, 4 H) 9,16 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 169



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



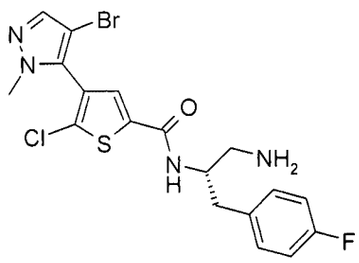
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxílico (183 mg, 0,54 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 167], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (201 mg, 0,52 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (298 mg, 0,64 mmol) en cloroformo (5 ml). Se añadió DIEA (470 µl, 2,69 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (246 mg, 0,36 mmol, 69%): LC-MS (ES) m/z = 653 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (246 mg, 0,38 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (0,083 ml, 2,64 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

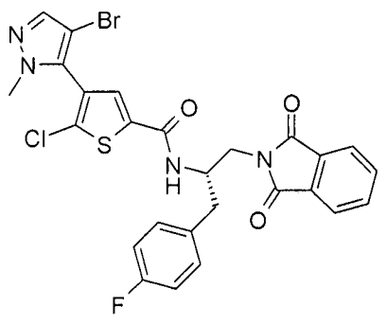
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (134 mg, 0,22 mmol, rendimiento de 57%): LC-MS (ES) m/z = 523 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 3,04 (d, J = 4,55 Hz, 4 H) 3,76 (s, 3 H) 4,29 - 443 (m, 1 H) 7,50 - 7,61 (m, 3 H) 7,66 (s, 1 H) 7,70 - 7,75 (m, 1 H) 8,06 - 8,18 (m, 4 H) 9,17 (s, 1 H).

Ejemplo 170



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxílico (340 mg, 1,00 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 167], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (374 mg, 1,12 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (626

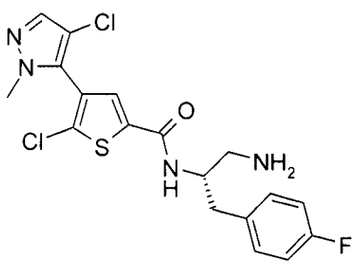
mg, 1,34 mmol) en cloroformo (10 ml). Se añadió DIEA (980 µl, 5,61 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (229 mg, 0,35 mmol, 31%): LC-MS (ES) m/z = 603 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-2-tiofenocarboxamida (229 mg, 0,38 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1,2 ml). Se añadió hidrazina (90 µl, 2,87 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

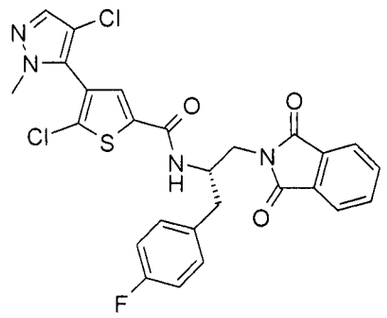
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (99 mg, 0,17 mmol, rendimiento de 45%): LC-MS (ES) m/z = 473 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,90 (d, *J* = 6,82 Hz, 2 H) 2,95 - 3,06 (m, 2 H) 3,77 (s, 3 H) 4,27 - 4,39 (m, 1 H) 7,11 (t, *J* = 8,72 Hz, 2 H) 7,26 - 7,35 (m, 2 H) 7,74 (s, 1 H) 8,01 - 8,21 (m, 4 H) 9,06 (s, 1 H).

Ejemplo 171



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-2-tiofenocarboxamida



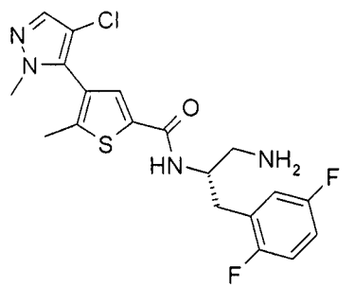
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (320 mg, 1,16 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 168], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (318 mg, 0,95 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (535 mg, 1,14 mmol) en cloroformo (9,5 ml). Se añadió DIEA (840 µl, 4,81 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (106 mg, 0,16 mmol, 17%): LC-MS (ES) m/z = 557 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-2-tiofenocarboxamida (106 mg, 0,19 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1,5 ml). Se añadió hidrazina (45 µl, 1,43 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

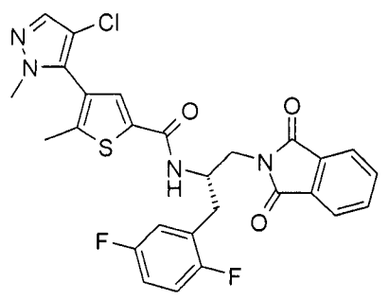
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (65 mg, 0,12 mmol, rendimiento de 65%): LC-MS (ES) m/z = 429 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,82 - 3,10 (m, 4 H) 3,77 (s, 3 H) 4,27 - 4,38 (m, 1 H) 7,11 (t, *J* = 8,72 Hz, 2 H) 7,26 - 7,35 (m, 2 H) 7,68 - 7,76 (m, 1 H) 8,10 (s, 4 H) 9,11 (d, *J* = 7,33 Hz, 1 H).

Ejemplo 172



Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (219 mg, 0,85 mmol) [preparada de acuerdo con el procedimiento del Ejemplo 158], 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (290 mg, 0,82 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (481 mg, 1,03 mmol) en cloroformo (8,5 ml). Se añadió DIEA (750

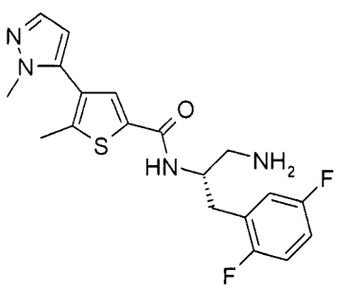
µl, 4,29 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (246 mg, 0,44 mmol, 52%): LC-MS (ES) m/z = 555 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-tiofenocarboxamida (246 mg, 0,44 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (100 µl, 3,19 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

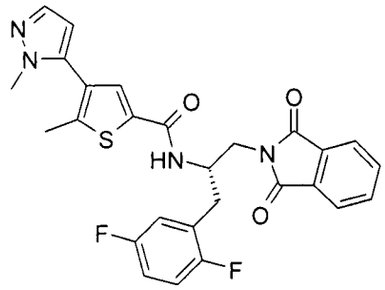
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (147 mg, 0,28 mmol, rendimiento de 64%): LC-MS (ES) m/z = 425 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,34 (s, 3 H) 2,93 - 3,07 (m, 4 H) 3,71 (s, 3 H) 4,34 - 4,50 (m, 1 H) 7,04 - 7,14 (m, 1 H) 7,19 (td, *J* = 9,03, 4,67 Hz, 2 H) 7,69 (s, 1 H) 7,93 (s, 1 H) 8,14 (s, 3 H) 8,87 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 173:



Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (171 mg, 0,77 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 151], 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (270 mg, 0,77 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (436 mg, 0,93 mmol) en cloroformo (7,5 ml). Se añadió DIEA (680 µl, 3,89 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (246 mg, 0,44 mmol, 52%): LC-MS (ES) m/z = 521 $(M+H)^+$.

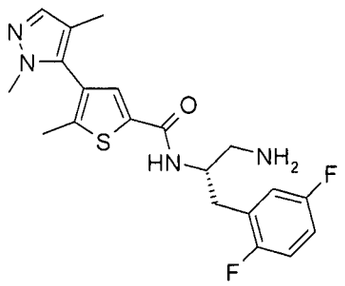
b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (243 mg, 0,47 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (0,103 ml, 3,27 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título

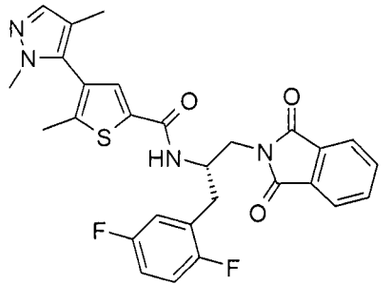
(132 mg, 0,27 mmol, rendimiento de 58%): LC-MS (ES) m/z = 391 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,38 (s, 3 H) 2,87 - 3,10 (m, 4 H) 3,78 (s, 3 H) 4,36 - 4,47 (m, 1 H) 6,35 (d, *J* = 1,77 Hz, 1 H) 7,05 - 7,13 (m, 1 H) 7,16 - 7,28 (m, 2 H) 7,52 (d, *J* = 1,52 Hz, 1 H) 8,00 (s, 1 H) 8,16 (s, 3 H) 8,88 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 174



Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) *N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxílico (208 mg, 0,88 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 164], 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (288 mg, 0,82 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (503 mg, 1,07 mmol) en cloroformo (8,5 ml). Se añadió DIEA (770 µl, 4,41 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc

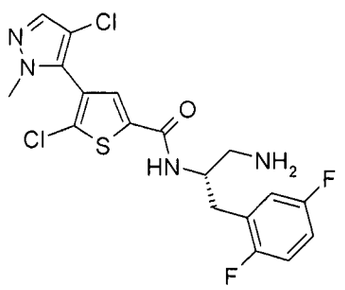
al 25 - 70%/Hex), produciendo el compuesto del título (292 mg, 0,55 mmol, 62%): LC-MS (ES) m/z = 535 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida (292 mg, 0,55 mmol) en tetrahidrofurano (THF) (5 ml) y metanol (1 ml). Se añadió hidrazina (120 µl, 3,82 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

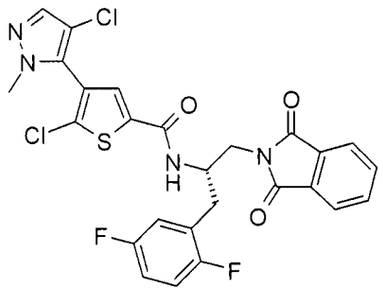
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (163 mg, 0,32 mmol, rendimiento de 59%): LC-MS (ES) m/z = 405 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 1,88 (s, 3 H) 2,27 (s, 3 H) 2,94 - 3,06 (m, 4 H) 3,63 (s, 3 H) 4,35 - 4,49 (m, 1 H) 7,05 - 7,12 (m, 1 H) 7,16 - 7,27 (m, 2 H) 7,38 (s, 1 H) 7,86 (s, 1 H) 8,16 (s, 3 H) 8,83 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 175



Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (235 mg, 0,85 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 96], 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (290 mg, 0,82 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (479 mg, 1,02 mmol) en cloroformo (8,5 ml). Se añadió DIEA (742 µl, 4,25 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (174 mg, 0,30 mmol, 36%): LC-MS (ES) m/z = 575 $(M+H)^+$.

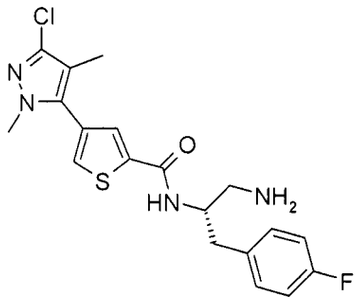
b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (174 mg, 0,30 mmol) en tetrahidrofurano (THF) (3,6 ml) y metanol (1 ml). Se añadió hidrazina (70 µl, 2,23 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (115 mg, 0,21 mmol, rendimiento de 70%): LC-MS (ES) m/z = 445 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,88 - 3,09 (m, 4 H) 3,76 (s, 3 H) 4,33 - 4,48 (m, 1 H)

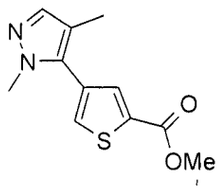
7,06 - 7,15 (m, 1 H) 7,20 (td, *J* = 9,09, 4,55 Hz, 2 H) 7,74 (s, 1 H) 8,10 (s, 1 H) 8,13 (s, 3 H) 9,14 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 176



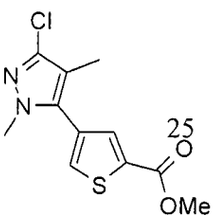
Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



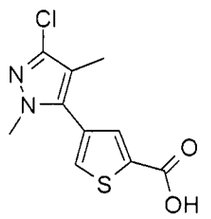
A un matraz reactor cerrado herméticamente de 350 ml se le añadieron 4-(4-bromo-1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (3,45 g, 11,46 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 156], trimetilboroxina (2,7 ml, 19,40 mmol), K_2CO_3 (4,75 g, 34,4 mmol) y $Pd(dppf)Cl_2$ (599 mg, 1,17 mmol) en N,N-dimetilformamida (DMF) (57 ml). La reacción se calentó a 110°C durante 1 hora, se enfrió a temperatura ambiente y se repartió entre $CHCl_3/H_2O$. La capa orgánica se separó, se secó con Na_2SO_4, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 0-30% /Hexano), produciendo el compuesto del título (2,07 g, 8,76 mmol, 76%): LC-MS (ES) m/z = 251 $(M+H)^+$.

b) 4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



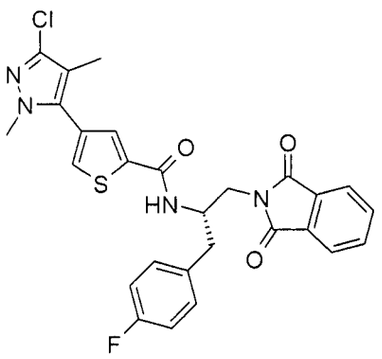
Se añadió en porciones NCS (1,78 g, 13,09 mmol) a un tubo reactor cerrado herméticamente de 125 ml que contenía 4-(1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,07 g, 8,76 mmol) en tetrahidrofurano (THF) (40 ml) a temperatura ambiente. La mezcla se calentó a 100°C durante 1 hora. Después de que se completara, el producto se repartió entre $CHCl_3$ y H_2O, la capa orgánica se secó con Na_2SO_4 y los disolventes se retiraron por destilación al vacío produciendo el compuesto del título (2,18 g, 7,97 mmol, 91%) que se usó sin purificación adicional: LC-MS (ES) m/z = 271 $(M+H)^+$.

c) ácido 4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (2,15 g, 7,94 mmol) en tetrahidrofurano (THF) (30 ml). Se añadió lentamente NaOH 6 N (30 ml, 180 mmol) y la reacción se agitó a 70°C durante una noche. La reacción se enfrió a temperatura ambiente, se repartió entre $CHCl_3$ y H_2O y el valor del pH de la capa acuosa se ajustó a ~3 mediante la adición de HCl 6 N. Las capas se separaron, la capa orgánica se secó con Na_2SO_4 y el disolvente se retiró produciendo el compuesto del título (1,35 g, 5,26 mmol, 66%) que se usó en la siguiente etapa sin purificación adicional LC-MS (ES) m/z = 257 $(M+H)^+$.

d) 4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxílico (294 mg, 1,14 mmol), 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (409 mg, 1,22 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (645 mg, 1,38 mmol) en cloroformo (10 ml). Se añadió DIEA (1 ml, 5,73 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (534 mg, 0,92 mmol, 81%): LC-MS (ES) m/z = 537 $(M+H)^+$.

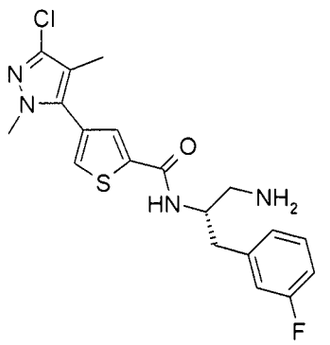
c) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-2-tiofenocarboxamida (534 mg, 0,994 mmol) en tetrahidrofurano (THF) (9 ml) y metanol (1 ml). Se añadió hidrazina (220 µl, 7,01 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla de reacción se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (354 mg, 0,70 mmol, rendimiento de 70%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^1H RMN

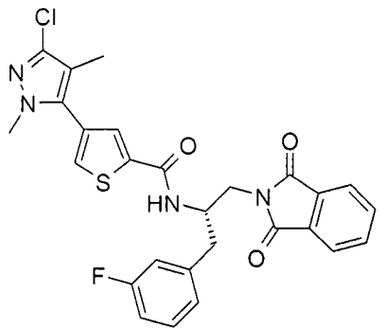
(400 MHz, DMSO-d_6) ppm 1,99 (s, 3 H) 2,91 - 3,02 (m, 4 H) 3,79 (s, 3 H) 4,30 - 4,41 (m, 1 H) 7,10 (t, J = 8,84 Hz, 2 H) 7,27 - 7,36 (m, 2 H) 8,01 (d, J = 1,26 Hz, 1 H) 8,15 (s, 3 H) 8,21 (d, J = 1,26 Hz, 1 H) 9,04 (d, J = 8,34 Hz, 1 H).

Ejemplo 177



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxílico (291 mg, 1,13 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 176], 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (409 mg, 1,22 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6 con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,8 mmol)] y PyBrop (654 mg, 1,39 mmol) en cloroformo (10 ml). Se añadió DIEA (1 ml, 5,73 mmol) y la

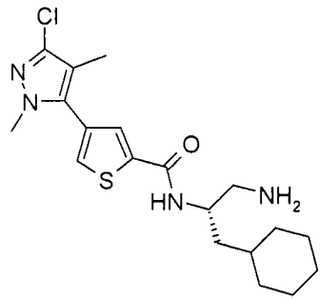
reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (427 mg, 0,76 mmol, 67%): LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (427 mg, 0,79 mmol) en tetrahidrofurano (THF) (7,5 ml) y metanol (1 ml). Se añadió hidrazina (175 µl, 5,58 mmol) y la solución se agitó a 25°C durante una noche. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

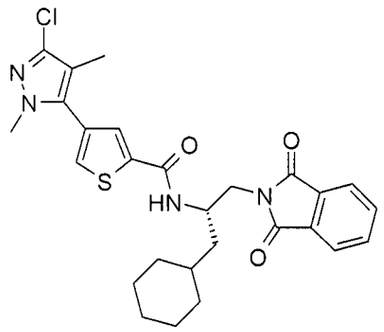
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (296 mg, 0,59 mmol, rendimiento de 74%): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 1,99 (s, 3 H) 2,95 - 3,06 (m, 4 H) 3,79 (s, 3 H) 4,33 - 4,45 (m, 1 H) 7,02 (td, *J* = 8,59, 2,02 Hz, 1 H) 7,09 - 7,18 (m, 2 H) 7,26 - 7,36 (m, 1 H) 8,01 (d, *J* = 1,01 Hz, 1 H) 8,16 (s, 3 H) 8,22 (s, 1 H) 9,07 (d, *J* = 8,34 Hz, 1 H).

Ejemplo 178



Preparación de *N*-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxílico (150 mg, 0,58 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 176], 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (176 mg, 0,54 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por 3-ciclohexil-N-{[(1,1-dimetiletil)oxi]carbonil}-L-alanina (5 g, 18,4 mmol)] y PyBrop (336 mg, 0,72 mmol) en cloroformo (6 ml). Se añadió DIEA (520 µl, 2,98 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (336 mg, 0,61 mmol, cuant.): LC-MS (ES) m/z = 526 $(M+H)^+$.

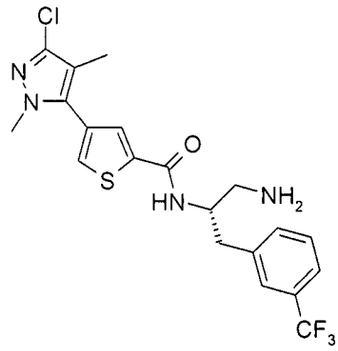
b) *N*-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-N-{(1S)-2-ciclohexil-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (366 mg, 0,697 mmol) en tetrahidrofurano (THF) (6,5 ml) y metanol (1 ml). Se añadió hidrazina (155 µl, 4,94 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título

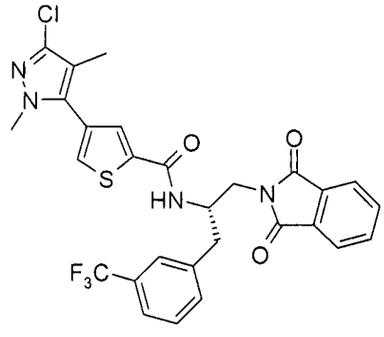
(173 mg, 0,35 mmol, rendimiento de 50%): LC-MS (ES) m/z = 395 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 0,80 - 0,92 (m, 1 H) 0,92 - 1,01 (m, 1 H) 1,13 (d, *J* = 6,57 Hz, 2 H) 1,22 (d, *J* = 12,88 Hz, 1 H) 1,29 (s, 1 H) 1,32 - 1,43 (m, 1 H) 1,48 - 1,56 (m, 1 H) 1,58 (d, *J* = 5,05 Hz, 1 H) 1,63 (s, 3 H) 1,73 - 1,84 (m, 1 H) 1,99 (s, 3 H) 2,94 (d, *J* = 5,31 Hz, 2 H) 3,78 (s, 3 H) 4,22 - 4,36 (m, 1 H) 8,03 (s, 1 H) 8,05 (s, 3 H) 8,19 (s, 1 H) 8,80 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 179



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxílico (238 mg, 0,93 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 176], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (355 mg, 0,92 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción

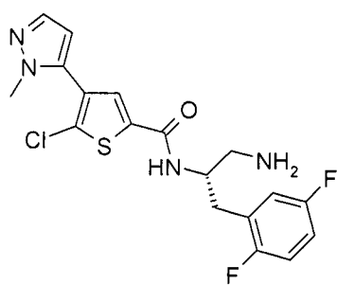
de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (5,0 g, 15,0 mmol)] y PyBrop (532 mg, 1,13 mmol) en cloroformo (9,5 ml). Se añadió DIEA (820 µl, 4,70 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (448 mg, 0,72 mmol, 78%): LC-MS (ES) m/z = 587 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (468 mg, 0,80 mmol) en tetrahidrofurano (THF) (7,5 ml) y metanol (1 ml). Se añadió hidrazina (175 µl, 5,58 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

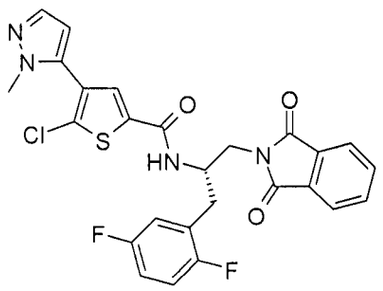
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (321 mg, 0,58 mmol, rendimiento de 72%): LC-MS (ES) m/z = 457 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 1,98 (s, 3 H) 3,05 (d, *J* = 7,07 Hz, 4 H) 3,77 (s, 3 H) 4,33 - 4,44 (m, 1 H) 7,49 - 7,57 (m, 2 H) 7,58 - 7,62 (m, 1 H) 7,66 (s, 1 H) 8,01 (d, *J* = 1,26 Hz, 1 H) 8,11 (s, 3 H) 8,17 (d, *J* = 1,26 Hz, 1 H) 9,02 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 180



Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-*N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



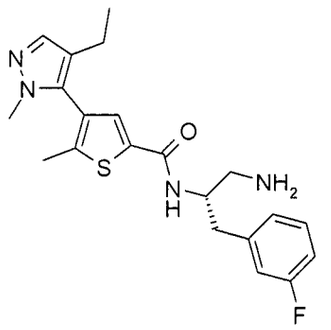
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (147 mg, 0,61 mmol), 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (216 mg, 0,61 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (341,4 mg, 0,73 mmol) en cloroformo (6 ml). Se añadió DIEA (530 µl, 3,03 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (233 mg, 0,43 mmol, 71%): LC-MS (ES) m/z = 541 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (233 mg, 0,43 mmol) en tetrahidrofurano (THF) (5 ml) y metanol (1 ml). Se añadió hidrazina (95 µl, 3,03 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (165 mg, 0,32 mmol, rendimiento de 75%): LC-MS (ES) m/z = 411 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,88 - 3,14 (m, 4 H) 3,85 (s, 3 H) 4,37 - 4,50 (m, 1 H) 6,48 (d, *J* = 1,77 Hz, 1 H) 7,09 (t, *J* = 8,34 Hz, 1 H) 7,19 (dt, *J* = 9,09, 4,55 Hz, 1 H) 7,29 (ddd, *J* = 8,84, 5,68, 3,16 Hz, 1 H) 7,55 (d, *J* = 1,52 Hz, 1 H) 8,22 (s, 3 H) 8,27 (s, 1 H) 9,32 (d, *J* = 8,84 Hz, 1 H).

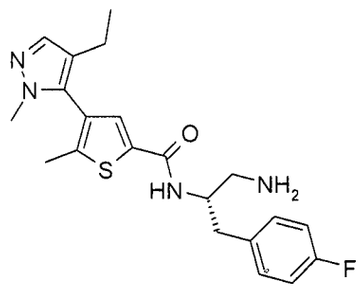
Ejemplo 181



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó de acuerdo con el procedimiento del Ejemplo 109, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona [preparada de acuerdo con la Preparación 6] por 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (184 mg, 0,55 mmol): LC-MS (ES) m/z = 401 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 1,04 (t, *J* = 7,33 Hz, 3 H) 2,13 - 2,33 (m, 5 H) 2,86 - 3,08 (m, 4 H) 3,60 (s, 3 H) 4,27 - 4,43 (m, 1 H) 6,96 - 7,07 (m, 1 H) 7,11 (d, *J* = 6,32 Hz, 2 H) 7,30 (s, 1 H) 7,43 (s, 1 H) 7,85 (s, 1 H) 8,19 (s, 3 H) 8,85 (s, 1 H).

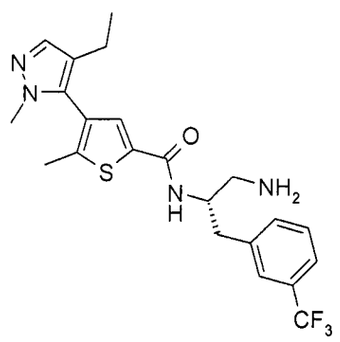
Ejemplo 182



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó de acuerdo con el procedimiento del Ejemplo 109, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona [preparada de acuerdo con la Preparación 6] por 2-[(2S)-2-amino-3-(3-fluorofenil)propil], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (207 mg, 0,62 mmol): LC-MS (ES) m/z = 401 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 1,04 (t, *J* = 7,20 Hz, 3 H) 2,25 (s, 5 H) 2,88 - 3,00 (m, 4 H) 3,61 (s, 3 H) 4,25 - 4,40 (m, 1 H) 7,01 - 7,17 (m, 2 H) 7,26 - 7,35 (m, 2 H) 7,42 (s, 1 H) 7,82 (s, 1 H) 8,17 (s, 3 H) 8,81 (s, 1 H).

Ejemplo 183

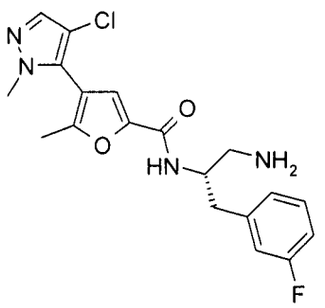


Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó de acuerdo con el procedimiento del Ejemplo 109, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona [preparada de acuerdo con la

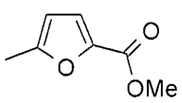
Preparación 6] por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (158 mg, 0,41 mmol): LC-MS (ES) m/z = 451 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 1,04 (t, *J* = 7,33 Hz, 3 H) 2,24 (s, 5 H) 3,03 (d, *J* = 6,32 Hz, 4 H) 3,59 (s, 3 H) 4,35 (s, 1 H) 7,42 (s, 1 H) 7,46 - 7,57 (m, 2 H) 7,59 (d, *J* = 6,57 Hz, 1 H) 7,64 (s, 1 H) 7,84 (s, 1 H) 8,20 (s, 3 H) 8,88 (s, 1 H).

Ejemplo 184



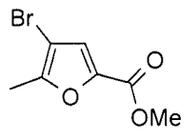
Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

a) 5-metil-2-furanocarboxilato de metilo



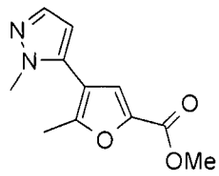
A un matraz de fondo redondo de 200 ml con condensador se le añadió ácido 5-metil-2-furanocarboxílico (2,5 g, 19,82 mmol) en metanol (100 ml). Se añadió lentamente H_2SO_4 (10,5 ml, 197 mmol) a temperatura ambiente. La mezcla de reacción se calentó a 50°C durante una noche. La mezcla de reacción se enfrió a 0°C y se añadió una solución saturada de $NaHCO_3$ a pH neutro seguido de NaOH 5 N a un valor de pH de 10. Se añadió $CHCl_3$ y la fase orgánica se separó, se secó con Na_2SO_4 y se concentró, produciendo el compuesto del título (2,3 g, 16,3 mmol, 82%): LC-MS (ES) m/z = 141 $(M+H)^+$.

b) 4-bromo-5-metil-2-furanocarboxilato de metilo



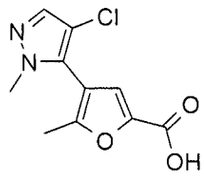
A una solución de 5-metil-2-furanocarboxilato de metilo (2,33 g, 16,29 mmol) y cloruro de aluminio (3,3 g, 24,75 mmol) en cloroformo (50 ml) a temperatura ambiente se le añadió Br_2 (1,1 ml, 21,35 mmol). La solución resultante se agitó a temperatura ambiente en un tubo reactor cerrado herméticamente de 150 ml durante 2 horas. Después de que se completara, la solución se enfrió en un baño de hielo, se añadió H_2O y la reacción se repartió entre $CHCl_3/H_2O$. La capa orgánica se lavó con $NaHCO_3$ y después con $Na_2S_2O_3$. La capa orgánica se secó con Na_2SO_4, se concentró, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 0-20%/Hexanos), produciendo el compuesto del título (2,13 g, 9,72 mmol, 60%): LC-MS (ES) m/z = 221 $(M+H)^+$.

c) 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



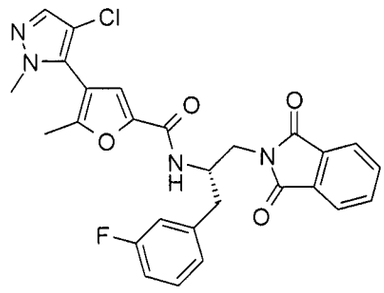
A un matraz reactor cerrado herméticamente de 5 ml se le añadieron 4-bromo-5-metil-2-furanocarboxilato de metilo (1,13 g, 5,16 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (1,31 g, 6,30 mmol) [preparado de acuerdo con el procedimiento de la Preparación 7], K_3PO_4 (3,87 g, 18,23 mmol), $Pd_2(dba)_3$ (153 mg, 0,17 mmol) y $P(OMe)_3$ (32 µl, 0,27 mmol) en 1,4-dioxano (23 ml). La reacción se calentó a 95°C durante 4 horas, se enfrió a temperatura ambiente y se repartió entre $CHCl_3/H_2O$. La capa orgánica se separó, se secó con Na_2SO_4, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 0-15%/Hexanos), produciendo el compuesto del título (967 mg, 4,39 mmol, 85%): LC-MS (ES) m/z = 271 $(M+H)^+$.

d) ácido 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxílico



Se añadió en porciones NCS (709 mg, 5,31 mmol) a un tubo reactor cerrado herméticamente de 150 ml que contenía 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (967 mg, 4,39 mmol) en tetrahidrofurano (THF) (20 ml) a temperatura ambiente. La mezcla se calentó a 70°C durante 1 hora. Después, se añadió NaOH 6 N (20 ml, 120 mmol) y la mezcla se agitó a 70°C durante 2 h más. La mezcla se repartió entre $CHCl_3$ y H_2O y el valor del pH de la fase acuosa se ajustó a ~3 con HCl 6 N. La capa orgánica se separó, se secó con Na_2SO_4 y se concentró, produciendo el compuesto del título (1,13 g, 4,41 mmol, cuant.) que se usó sin purificación adicional: LC-MS (ES) m/z = 241 $(M+H)^+$.

e) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-furanocarboxamida



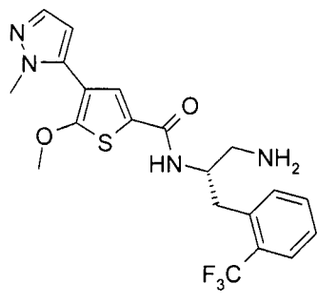
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (244 mg, 0,95 mmol), 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (320 mg, 0,95 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,0 g, 17,8 mmol)] y PyBrop (533 mg, 1,14 mmol) en cloroformo (9 ml). Se añadió DIEA (830 µl, 4,75 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (242 mg, 0,465 mmol, 49%): LC-MS (ES) m/z = 521 $(M+H)^+$.

f) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-metil-2-furanocarboxamida (238 mg, 0,46 mmol) en tetrahidrofurano (THF) (3,6 ml) y metanol (1 ml). Se añadió hidrazina (100 µl, 3,19 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

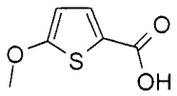
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (157 mg, 0,32 mmol, rendimiento de 71%): LC-MS (ES) m/z = 391 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,31 (s, 3 H) 2,91 - 3,03 (m, 4 H) 3,73 (s, 3 H) 4,36 - 4,49 (m, 1 H) 7,03 (t, *J* = 7,71 Hz, 1 H) 7,07 - 7,14 (m, 2 H) 7,29 - 7,37 (m, 1 H) 7,39 (s, 1 H) 7,67 (s, 1 H) 8,14 (s, 3 H) 8,65 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 185



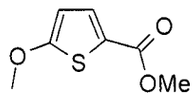
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 5-(metiloxi)-2-tiofenocarboxílico



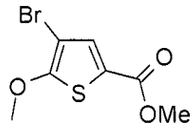
Se añadió lentamente 2-(metiloxi)tiofeno (1,01 g, 8,85 mmol) durante 15 min a un matraz de fondo redondo de 100 ml que contenía nBuLi 2,5 M en hexanos (3,8 ml, 9,50 mmol) en tetrahidrofurano (THF) (40 ml) a -78°C. Después de calentar a temperatura ambiente y de agitar durante 2 h, la mezcla se enfrió a -35°C y se añadió CO_2 sólido picado. La mezcla se calentó a temperatura ambiente durante 3 horas, se enfrió en un baño de hielo y se inactivó con NH_4Cl (sat.). La mezcla de reacción fría se repartió entre $CHCl_3/H_2O$ y la capa acuosa se hizo básica con HCl 6 N. La capa orgánica separada se secó con Na_2SO_4 y se concentró, produciendo el compuesto del título (1,3 g, 8,05 mmol, 91%) que se usó sin purificación adicional: LC-MS (ES) m/z = 159 $(M+H)^+$.

b) 5-(metiloxi)-2-tiofenocarboxilato de metilo



A un matraz de fondo redondo de 200 ml equipado con un condensador se le añadió ácido 5-(metiloxi)-2-tiofenocarboxílico (1,3 g, 8,22 mmol) en metanol (40 ml). Se añadió lentamente H_2SO_4 (5 ml, 94 mmol) a temperatura ambiente y la reacción se agitó a 50°C durante una noche. La mezcla se enfrió a 0°C y se añadió $NaHCO_3$ sat. a pH neutro seguido de NaOH 5 N a un valor de pH de 10. La mezcla se repartió entre $H_2O/CHCl_3$ y la fase orgánica se separó y se secó sobre Na_2SO_4. La solución se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 5-50%/Hexanos), produciendo el compuesto del título (827 mg, 4,56 mmol, 56%): LC-MS (ES) m/z = 173 $(M+H)^+$.

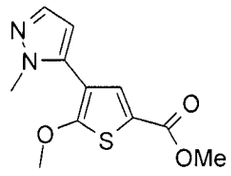
c) 4-bromo-5-(metiloxi)-2-tiofenocarboxilato de metilo



Se añadió en porciones NBS (903 mg, 5,07 mmol) a un tubo reactor cerrado herméticamente de 5 ml que contenía 5-(metiloxi)-2-tiofenocarboxilato de metilo (0,73 g, 4,23 mmol) en N,N-dimetilformamida (DMF) (20 ml) a temperatura ambiente y la reacción se agitó durante 1 hora. Se añadió más cantidad de NBS (249 mg) y después de 1 h a temperatura ambiente el producto se repartió entre $CHCl_3$ y H_2O. La capa orgánica se secó con Na_2SO_4, se adsorbió sobre sílice y se

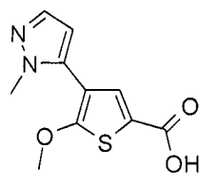
purificó por cromatografía en columna (EtOAc al 0-25%/Hexanos), produciendo el compuesto del título (825 mg, 3,19 mmol, 75%): LC-MS (ES) m/z = 252 $(M+H)^+$.

d) 5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



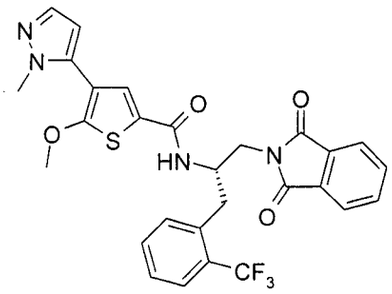
A un matraz reactor cerrado herméticamente de 350 ml se le añadieron 4-bromo-5-(metiloxi)-2-tiofenocarboxilato de metilo (772 mg, 3,07 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (773 mg, 3,72 mmol) [preparado de acuerdo con el procedimiento de la Preparación 7], K_2CO_3 (1,419 g, 10,27 mmol) y $Pd(Pt\text{-}Bu_3)_2$ (103 mg, 0,20 mmol) en 1,4-dioxano (12 ml) y agua (3 ml). La reacción se calentó a 85°C durante 2 horas. La mezcla se repartió entre $CHCl_3/H_2O$ y la capa acuosa se hizo básica con HCl 6 N. La capa orgánica separada se secó sobre Na_2SO_4 y se evaporó. El material resultante se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc 0-50%/Hexano), produciendo el compuesto del título (967 mg, 4,39 mmol, 85%): LC-MS (ES) m/z = 253 $(M+H)^+$.

e) ácido 5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 5-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (203 mg, 0,805 mmol) en tetrahidrofurano (THF) (4 ml). Se añadió lentamente NaOH 6 N (4 ml, 24,0 mmol) y la mezcla de reacción se agitó durante una noche a 70°C. La mezcla se neutralizó mediante la adición de HCl 6 N y se repartió entre $CHCl_3$ y H_2O. Las capas se separaron y la capa orgánica se secó sobre Na_2SO_4 y se concentró, produciendo el compuesto del título (152 mg, 0,64 mmol, 79%), que se usó en la siguiente etapa sin purificación adicional: LC-MS (ES) m/z = 239 $(M+H)^+$.

f) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (148 mg, 0,62 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (242 mg, 0,63 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y PyBrop (356 mg, 0,76 mmol) en cloroformo (6 ml). Se añadió DIEA (550 µl, 3,15 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (303 mg, 0,51 mmol, 82%): LC-MS (ES) m/z = 569 $(M+H)^+$.

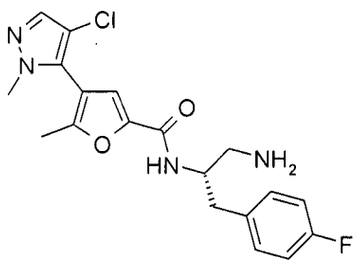
g) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (303 mg, 0,51 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (110 µl, 3,50 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (122 mg, 0,23 mmol, rendimiento de 45%): LC-MS (ES) m/z = 439 $(M+H)^+$, ^{1}H RMN

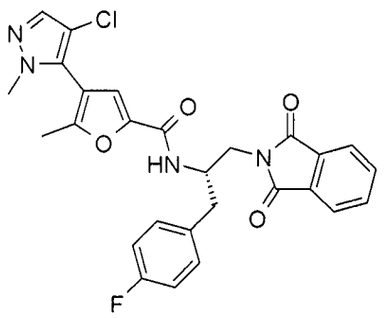
(400 MHz, DMSO-d_6) ppm 2,93 - 3,02 (m, 1 H) 3,03 - 3,14 (m, 3 H) 3,82 (s, 3 H) 3,98 (s, 3 H) 4,41 - 4,53 (m, 1 H) 6,32 (s, 1 H) 7,38 - 7,49 (m, 2 H) 7,52 - 7,63 (m, 2 H) 7,68 (d, *J* = 7,58 Hz, 1 H) 8,01 (s, 1 H) 8,17 (s, 3 H) 8,93 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 186



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-furanocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (248 mg, 0,97 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 184], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (321 mg, 0,96 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (557 mg, 1,19 mmol) en cloroformo (9,5 ml). Se añadió DIEA (840 µl, 4,81 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 -

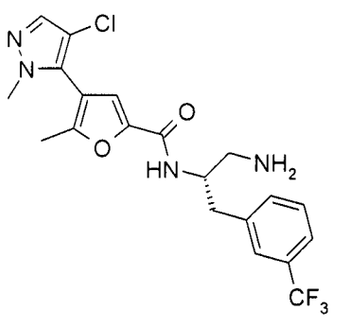
70%/Hex), produciendo el compuesto del título (167 mg, 0,26 mmol, 67%): LC-MS (ES) m/z = 521 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-metil-2-furanocarboxamida (144 mg, 0,27 mmol) en tetrahidrofurano (THF) (2,5 ml) y metanol (1 ml). Se añadió hidrazina (60 µl, 1,91 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

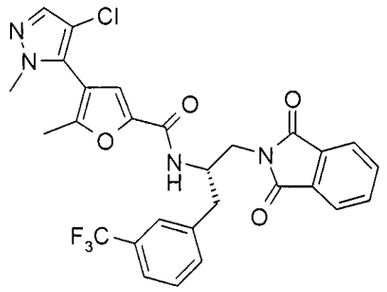
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (100 mg, 0,21 mmol, rendimiento de 74%): LC-MS (ES) m/z = 391 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,31 (s, 3 H) 2,83 - 2,93 (m, 2 H) 2,94 - 3,04 (m, 2 H) 3,73 (s, 3 H) 4,32 - 4,44 (m, 1 H) 7,12 (t, *J* = 8,59 Hz, 2 H) 7,25 - 7,33 (m, 2 H) 7,35 (s, 1 H) 7,67 (s, 1 H) 8,07 (s, 3 H) 8,57 (d, *J* = 8,59 Hz, 1 H).

Ejemplo 187



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida



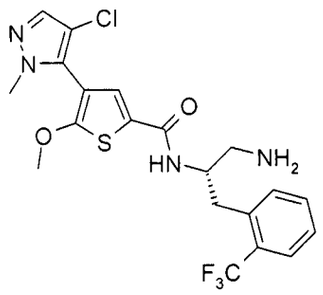
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (230 mg, 0,90 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 184], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (348 mg, 0,90 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (502 mg, 1,07 mmol) en cloroformo (8,5 ml). Se añadió DIEA (790 µl, 4,52 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (247 mg, 0,43 mmol, 48%): LC-MS (ES) m/z = 571 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-2-furanocarboxamida (247 mg, 0,433 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (95 µl, 3,03 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

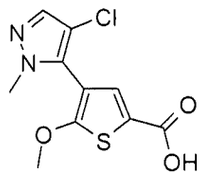
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (206 mg, 0,38 mmol, rendimiento de 88%): LC-MS (ES) m/z = 441 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,30 (s, 3 H) 2,97 - 3,08 (m, 4 H) 3,71 (s, 3 H) 4,35 - 4,49 (m, 1 H) 7,36 (s, 1 H) 7,54 (dt, *J* = 19,20, 7,20 Hz, 3 H) 7,62 - 7,68 (m, 2 H) 8,14 (s, 3 H) 8,65 (d, *J* = 8,84 Hz, 1 H).

Ejemplo 188



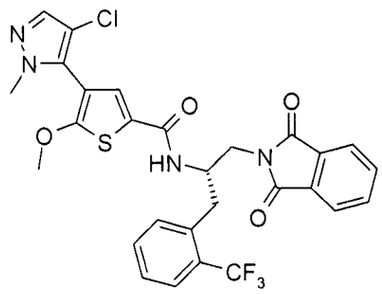
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

a) ácido 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxílico



Se añadió en porciones NCS (382 mg, 2,80 mmol) a un tubo reactor cerrado herméticamente de 50 ml que contenía 5-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (642 mg, 2,54 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 185] en tetrahidrofurano (THF) (12 ml) a temperatura ambiente. La mezcla se calentó a 70°C durante 1 hora. La reacción se enfrió a temperatura ambiente, se añadió NaOH 6 N (10 ml, 60,0 mmol) y la mezcla se agitó durante 3 h más a 70°C. La mezcla se repartió entre $CHCl_3$ y H_2O y la capa acuosa se hizo básica con HCl 6 N. La capa orgánica se secó sobre Na_2SO_4 y se concentró, produciendo el compuesto del título (759 mg, 2,51 mmol, 98%) que se usó sin purificación adicional: LC-MS (ES) m/z = 273 $(M+H)^+$.

b) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxílico (85 mg, 0,31 mmol), 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (119 mg, 0,31 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y PyBrop (180 mg, 0,384 mmol) en cloroformo (3,5 ml). Se añadió DIEA (270 µl, 1,54 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (94 mg, 0,14 mmol, 45%): LC-MS (ES) m/z = 603 $(M+H)^+$.

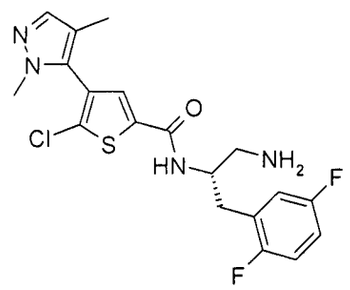
c) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-2-tiofenocarboxamida (94 mg, 0,16 mmol) en tetrahidrofurano (THF) (2 ml) y metanol (1 ml). Se añadió hidrazina (35 µl, 1,12 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (27 mg, 0,05 mmol, rendimiento de 31%): LC-MS (ES) m/z = 473 $(M+H)^+$, ^{1}H RMN

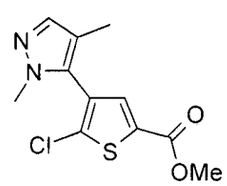
(400 MHz, DMSO-d_6) ppm 2,93 - 3,14 (m, 4 H) 3,73 (s, 3 H) 4,00 (s, 3 H) 4,41 - 4,54 (m, 1 H) 7,43 (t, *J* = 7,45 Hz, 1 H) 7,57 (ddd, *J* = 14,59, 7,58, 7,39 Hz, 2 H) 7,62 - 7,65 (m, 1 H) 7,69 (d, *J* = 7,83 Hz, 1 H) 7,82 - 7,89 (m, 1 H) 8,12 (s, 3 H) 8,80 (d, *J* = 9,09 Hz, 1 H).

Ejemplo 189



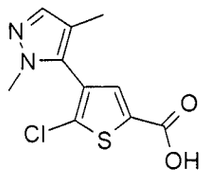
Preparación de *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



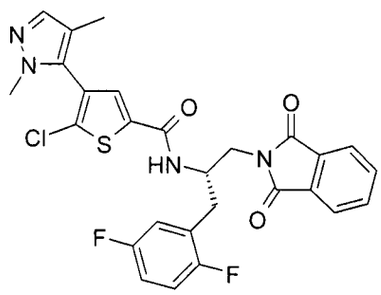
A un matraz reactor cerrado herméticamente de 350 ml se le añadieron 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (409 mg, 1,60 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 95], 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (388 mg, 1,75 mmol) [preparado de acuerdo con el procedimiento de la Preparación 17], K_2CO_3 (676 mg, 4,89 mmol) y $Pd(PtBu_3)_2$ (32 mg, 0,06 mmol) en 1,4-dioxano (6 ml) y agua (1,5 ml). La reacción se calentó a 85°C durante 3 horas. La reacción se repartió entre $CHCl_3/H_2O$ y el valor del pH de la capa acuosa se ajustó a ~3 con HCl 6 N. La capa orgánica separada se secó con Na_2SO_4, se adsorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 10-65%/Hexanos), produciendo el compuesto del título (106 mg, 0,39 mmol,%); LC-MS (ES) m/z = 271 $(M+H)^+$.

b) ácido 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A un matraz de fondo redondo de 100 ml se le añadió 5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (106 mg, 0,39 mmol) en tetrahidrofurano (THF) (2 ml). Se añadió lentamente NaOH 6 N (2 ml, 12,00 mmol) y la mezcla de reacción se agitó durante una noche a 70°C. La reacción se enfrió a temperatura ambiente, se repartió entre $CHCl_3$ y H_2O y el valor del pH de la capa acuosa se ajustó a ~3 mediante la adición de HCl 6 N. Las capas se separaron, la capa orgánica se secó sobre Na_2SO_4 y se concentró, produciendo el compuesto deseado (96 mg, 0,37 mmol, 95%): LC-MS (ES) m/z = 257 $(M+H)^+$.

c) 5-cloro-*N*-{(1*S*)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



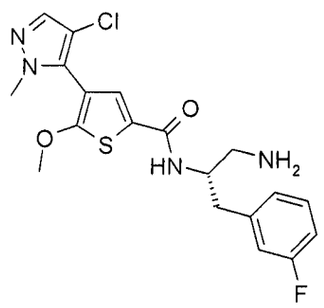
A un matraz de fondo redondo de 50 ml se le añadieron ácido 5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxílico (96 mg, 0,37 mmol), 2-[(2S)-2-amino-3-(2,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (125 mg, 0,40 mmol) [preparada de acuerdo con el procedimiento de la Preparación 18 con la excepción de que se sustituyó 2,6-difluoro-L-fenilalanina por 2,5-difluoro-L-fenilalanina (3,02 g, 15,0 mmol)] y PyBrop (225 mg, 0,48 mmol) en cloroformo (4 ml). Se añadió DIEA (330 µl, 1,89 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (98 mg, 0,13 mmol, 34%): LC-MS (ES) m/z = 535 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 5-cloro-N-{(1S)-2-(2,5-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-4-(1,4-dimetil-1H-pirazol-5-il)-2-tiofenocarboxamida (98 mg, 0,18 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1 ml). Se añadió hidrazina (40 µl, 1,27 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de CHCl3/MeOH/NH4OH).

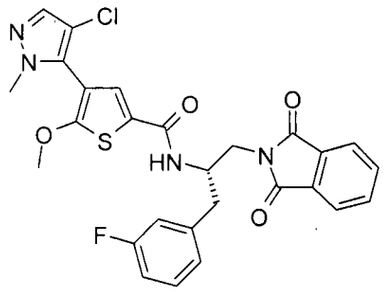
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (52 mg, 0,10 mmol, rendimiento de 56%): LC-MS (ES) m/z = 425 (M+H)+, ^{1}H RMN (400 MHz, DMSO-d6) ppm 1,94 (s, 3 H) 2,87 - 3,09 (m, 4 H) 3,69 (s, 3 H) 4,42 (d, J = 6,32 Hz, 1 H) 7,10 (ddd, J = 12,00, 8,34, 3,41 Hz, 1 H) 7,20 (td, J = 9,16, 4,67 Hz, 1 H) 7,27 (ddd, J = 8,97, 5,56, 3,16 Hz, 1 H) 7,39 (s, 1 H) 8,06 (s, 1 H) 8,13 (s, 3 H) 9,13 (d, J = 8,84 Hz, 1 H).

Ejemplo 190



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-(metiloxi)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxílico (220 mg, 0,81 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 188], 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (281 mg, 0,84 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-fluoro-L-fenilalanina (5,03 g, 17,8 mmol)] y PyBrop (472 mg, 1,0 mmol) en cloroformo (8 ml). Se añadió DIEA (710 µl, 4,07 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (281 mg, 0,51 mmol, 63%): LC-MS (ES) m/z = 553 $(M+H)^+$.

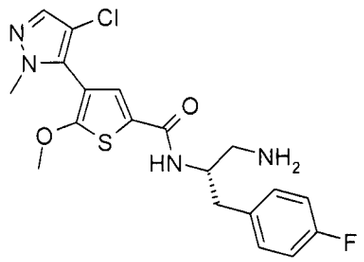
b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-5-(metiloxi)-2-tiofenocarboxamida (281 mg, 0,51 mmol) en tetrahidrofurano (THF) (4,5 ml) y metanol (1 ml). Se añadió hidrazina (120 µl, 3,82 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (145 mg, 0,28 mmol, rendimiento de 55%): LC-MS (ES) m/z = 423 $(M+H)^+$, ^{1}H RMN

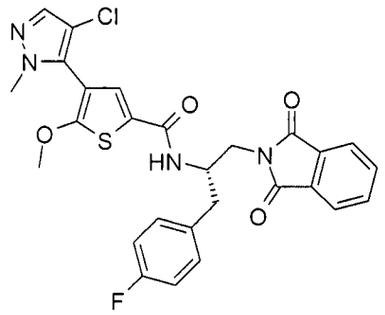
(400 MHz, DMSO-d_6) ppm 2,86 - 3,04 (m, 4 H) 3,71 (s, 3 H) 4,02 (s, 3 H) 4,31 - 4,41 (m, 1 H) 7,00 - 7,07 (m, 1 H) 7,11 (d, J = 7,58 Hz, 2 H) 7,28 - 7,36 (m, 1 H) 7,64 (s, 1 H) 7,73 - 7,78 (m, 1 H) 7,98 (s, 3 H) 8,54 (s, 1 H).

Ejemplo 191



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-(metiloxi)-2-tiofenocarboxamida



A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxílico (208 mg, 0,76 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 188], 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (257 mg, 0,77 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-4-fluoro-L-fenilalanina (4,95 g, 17,5 mmol)] y PyBrop (435 mg, 0,93 mmol) en cloroformo (7,6 ml). Se añadió DIEA (670 µl, 3,84 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 -

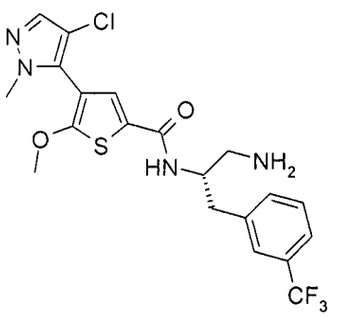
70%/Hex), produciendo el compuesto del título (238 mg, 0,43 mmol, 56%): LC-MS (ES) m/z = 553 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-(metiloxi)-2-tiofenocarboxamida (238 mg, 0,43 mmol) en tetrahidrofurano (THF) (4 ml) y metanol (1 ml). Se añadió hidrazina (95 µl, 3,03 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

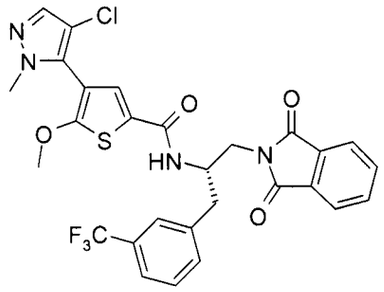
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (113 mg, 0,22 mmol, rendimiento de 50%): LC-MS (ES) m/z = 423 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 2,82 - 2,92 (m, 2 H) 2,93 - 3,03 (m, 2 H) 3,71 (s, 3 H) 4,02 (s, 3 H) 4,26 - 4,37 (m, 1 H) 7,11 (t, *J* = 8,46 Hz, 2 H) 7,26 - 7,32 (m, 2 H) 7,64 (s, 1 H) 7,69 - 7,84 (m, 1H) 7,95 (s, 3 H) 8,45 - 8,52 (m, 1H).

Ejemplo 192



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

a) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-2-tiofenocarboxamida



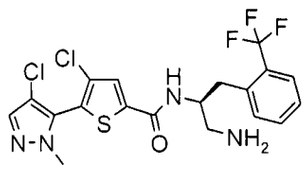
A un matraz de fondo redondo de 50 ml se le añadieron ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxílico (210 mg, 0,77 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 188], 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (294 mg, 0,764 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6, con la excepción de que se sustituyó N-{[(1,1-dimetiletil)oxi]carbonil}-2-(trifluorometil)-L-fenilalanina por *N*-{[(1,1-dimetiletil)oxi]carbonil}-3-(trifluorometil)-L-fenilalanina (4,98 g, 15,0 mmol)] y PyBrop (442 mg, 0,94 mmol) en cloroformo (7,6 ml). Se añadió DIEA (670 µl, 3,84 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre sílice y se purificó por cromatografía en columna (EtOAc al 25 - 70%/Hex), produciendo el compuesto del título (238 mg, 0,43 mmol, 56%): LC-MS (ES) m/z = 603 $(M+H)^+$.

b) *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida

A un matraz de fondo redondo de 50 ml se le añadió 4-(4-cloro-1-metil-1H-pirazol-5-il)-N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[3-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-2-tiofenocarboxamida (203 mg, 0,34 mmol) en tetrahidrofurano (THF) (3 ml) y metanol (1 ml). Se añadió hidrazina (80 µl, 2,55 mmol) y la reacción se agitó durante una noche a temperatura ambiente. La mezcla se absorbió sobre gel de sílice y se purificó por cromatografía en columna (90:10:1 de $CHCl_3$/MeOH/NH_4OH).

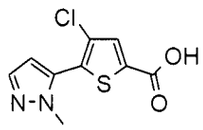
El compuesto neutro se disolvió en MeOH (2 ml), se trató con un exceso de HCl 2 M en Et_2O y se concentró, produciendo la sal HCl del compuesto del título (86 mg, 0,15 mmol, rendimiento de 44%): LC-MS (ES) m/z = 473 $(M+H)^+$, ^1H RMN (400 MHz, DMSO-d_6) ppm 2,92 - 3,08 (m, 4 H) 3,70 (s, 3 H) 4,01 (s, 3 H) 4,30 - 4,42 (m, 1 H) 7,50 - 7,60 (m, 3 H) 7,61 - 7,66 (m, 2 H) 7,73 - 7,81 (m, 1H) 8,00 (s, 3 H) 8,52 - 8,68 (m, 1H).

Ejemplo 193



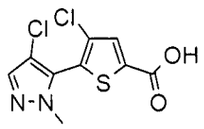
Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) ácido 4-cloro-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



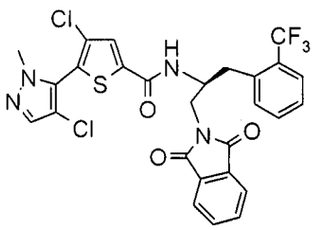
A una solución de ácido 5-bromo-4-cloro-2-tiofenocarboxílico (482 mg, 2 mmol) en dioxano/H_2O (4:1, 10 ml) se le añadieron complejo de 1,1'-bis(difenilfosfino)ferrocenodicloropaladio (II) y diclorometano (16,3 mg, 0,02 mmol), carbonato potásico (828 mg, 6 mmol) y 5-(5,5-dimetil-1,3,2-dooxaborinan-2-il)-1-metil-1*H*-pirazol (832 mg, 4 mmol) [preparado de acuerdo con la Preparación 7]. La mezcla de reacción se calentó a 80°C en un tubo cerrado herméticamente durante 20 h. La mezcla de reacción se vertió en H_2O (100 ml) y se extrajo con DCM. La capa orgánica se secó sobre Na_2SO_4, se concentró y se purificó usando sílice (EtOAc/hexano (gradiente al 0 – 45%)), produciendo el compuesto del título en forma de un sólido de color blanco (401,7 mg, 83%): LC-MS (ES) m/z = 243 $(M+H)^+$.

b) ácido 4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



Una solución de ácido 4-cloro-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (121 mg, 0,5 mmol) y N-clorosuccinimida (67 mg, 0,5 mmol) en THF (5 ml) se agitó en un tubo cerrado herméticamente a 70ºC. Después de 4 h, la solución se concentró y se repartió entre DCM y H_2O. La capa acuosa se extrajo varias veces con DCM. Las fracciones orgánicas se combinaron, se concentraron y se secaron azeotrópicamente con tolueno para dar el compuesto del título en forma de un aceite pardo (136 mg, 98%): LC-MS (ES) m/z = 278 $(M+H)^+$.

c). 4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida

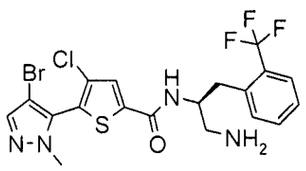


A una solución de ácido 4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (136,1 mg, 0,49 mmol), 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (179 mg, 0,51 mmol) [preparada de acuerdo con la Preparación 6] y diisopropiletil amina (260 µl, 1,5 mmol) en DCM (5 ml) se le añadió en una porción PyBrop (341 mg, 0,75 mmol). Después de 1 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, gradiente de acetato de etilo al 0- 50%/hexano), produciendo el compuesto del título (242 mg, 82%) en forma de un sólido de color blanco: LCMS (ES) m/z = 607 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A una solución de 4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (242 mg, 0,4 mmol) en THF-MeOH (1:1, 4 ml) se le añadió gota a gota hidrazina (75 µl, 2,42 mmol). Después de 12 h, la solución se concentró. El residuo resultante se repartió entre DCM y H_2O. Los extractos orgánicos se lavaron tres veces con agua y se acidificaron a un valor de pH de ~1 con una solución acuosa 6 N de HCl. La mezcla resultante se extrajo con agua. Las fracciones acuosas se combinaron y se concentraron para producir la sal di-HCl del producto deseado en forma de un sólido de color amarillo claro (77 mg, 40%): LCMS (ES) m/z 477 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 3,08-3,11 (m, 4 H) 3,75 (s, 3 H) 4,50 (s a, 1 H) 7,45 (t, *J* = 6,95 Hz, 1H) 7,55 - 7,63 (m, 2H) 7,71 (d, *J* = 7,83 Hz, 1 H) 7,78 (s, 1 H) 8,02 - 8,10 (m, 3 H) 8,12 (s, 1 H) 9,12 (d, *J* = 9,09 Hz, 1 H)

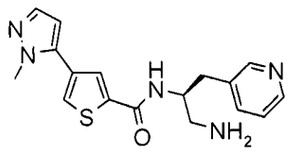
Ejemplo 194



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo claro de acuerdo con el procedimiento del Ejemplo 193, con la excepción de que se sustituyó N-clorosuccinimida por N-bromosuccinimida (89 mg, 0,5 mmol): LCMS (ES) m/z 522 $(M+H)^+$, ^{1}H RMN (400 MHz, DMSO-d_6) ppm 3,0-3,13 (m, 4 H) 3,76 (s, 3 H) 4,50 (s a, 1 H) 7,46 (d, *J* = 7,58 Hz, 1 H) 7,55 - 7,66 (m, 2 H) 7,71 (d, *J* = 7,83 Hz, 1 H) 7,78 (s, 1 H) 8,04 (s a, 4 H).

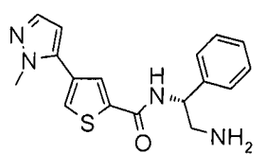
Ejemplo 195



Preparación de *N*-[(1*S*)-2-amino-1-(3-piridinilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo claro de acuerdo con el procedimiento del Ejemplo 6, con la excepción de que se sustituyó ácido 5-bromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (62 mg, 0,3 mmol) y se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona-HCl por 2-[(2*S*)-2-amino-3-(3-piridinil)propil]-1*H*-isoindolo-1,3(2*H*)-diona-HCl (84 mg, 0,3 mmol) [preparada de acuerdo con la Preparación 19]: LC-MS (ES) m/z = 342 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) ppm 3,17 (dd, *J* = 13,89, 10,86 Hz, 1 H) 3,33 - 3,36 (m, 2 H) 3,36 - 3,44 (m, 1 H) 3,96 (s, 3 H) 4,70 (dd, *J* = 14,02, 6,19 Hz, 1 H) 6,47 (s, 1 H) 7,51 (s, 1 H) 7,88 (d, *J* = 1,26 Hz, 1 H) 7,94 (s, 1 H) 8,02 (t, *J* = 6,32 Hz, 1 H) 8,61 (d, *J* = 7,83 Hz, 1 H) 8,76 (s a, 1 H) 8,89 (s a, 1 H).

Ejemplo 196

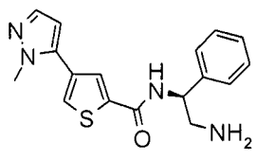


Preparación de *N*-[(1*R*)-2-amino-1-feniletil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó ácido 4,5-dibromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (83 mg, 0,4 mmol) y se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por [(2*R*)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo (94 mg, 0,4 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1]: LC-MS (ES) m/z = 327 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) ppm 3,44 (d, *J* = 4,29 Hz, 1 H) 3,63 (s a, 1 H)

4,18 (s, 3 H) 5,47 (dd, *J* = 10,36, 4,55 Hz, 1 H) 6,88 (d, *J* = 2,78 Hz, 1 H) 7,38 (d, *J* = 7,07 Hz, 1 H) 7,44 (t, *J* = 7,33 Hz, 2 H) 7,55 (d, *J* = 7,83 Hz, 2 H) 8,08 (d, *J* = 2,53 Hz, 1 H) 8,18 (d, *J* = 1,26 Hz,1 H) 8,42 (d, *J* = 1,26 Hz, 1 H).

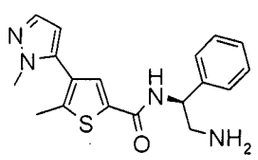
Ejemplo 197:



Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

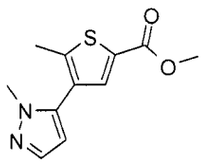
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 20, con la excepción de que se sustituyó ácido 4,5-dibromo-2-tiofenocarboxílico por ácido 4-bromo-2-tiofenocarboxílico (83 mg, 0,4 mmol) y se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo (94 mg, 0,4 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1]: LC-MS (ES) m/z 327 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,44 (d, J = 2,78 Hz, 1 H) 3,60 (s a, 1 H) 4,06 (s a, 3 H) 5,47 (dd, J = 10,36, 4,29 Hz, 1 H) 6,70 (s a, 1 H) 7,38 (d, J = 6,82 Hz, 1 H) 7,44 (t, J = 7,20 Hz, 2 H) 7,53 (d, J = 7,58 Hz, 2 H) 7,79 (s a, 1 H) 8,04 (s a,1 H) 8,32 (s a, 1 H).

Ejemplo 198:



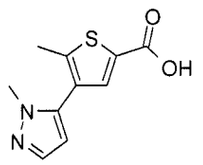
Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



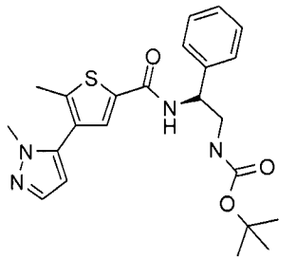
Una solución de 4-bromo-5-metil-2-tiofenocarboxilato de metilo (2 g, 8,51 mmol) [preparado en la Preparación 10], carbonato potásico (5,88 g, 42,5 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,12 g, 10,21 mmol) [preparado de acuerdo con la Preparación 7] y bis(tri-t-butilfosfina)paladio (0) (0,22 g, 0,43 mmol) en 1,4-dioxano (35 ml) y H_2O (7 ml) se agitó a 80°C en un tubo cerrado herméticamente durante 1 h. Después, la mezcla de reacción se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 25% en hexanos), produciendo 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo. Esta reacción se realizó en varias extracciones (1 g, 3 x 2 g) que se combinaron para el tratamiento y se purificaron, produciendo el compuesto del título (5,5 g, rendimiento combinado de 78%) en forma de un aceite viscoso de color amarillo: LC-MS (ES) m/e 236 $(M+H)^+$.

b) ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



Una solución de 5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (94 mg, 0,4 mmol) en hidróxido sódico 6 N (0,67 ml, 4 mmol) y tetrahidrofurano (4 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~3 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo el producto deseado (67 mg, 0,3 mmol, rendimiento de 75%) en forma de un aceite de color amarillo: LC-MS (ES) m/e 223 (M+H)+.

c) [(2S)-2-({[5-metil-4-(1-metil-1H-pirazol-5-il)-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo

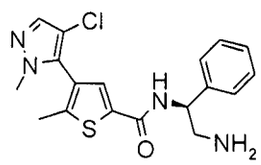


A una solución de ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (67 mg, 0,3 mmol), [(2*S*)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo (71 mg, 0,3 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1] y diisopropiletilamina (0,16 ml, 0,9 mmol) en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (210 mg, 0,45 mmol). La solución se agitó a 25ºC durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo el compuesto del título (87 mg, 0,2 mmol, rendimiento de 65%) en forma de una espuma amarilla: LC-MS (ES) m/e 441 (M+H)+.

d) *N*-[(1*S*)-2-amino-1-feniletil]-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A una solución de [(2*S*)-2-({[4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo (87 mg, 0,2 mmol) en DCM (2 ml) se le añadió una solución 4 N de HCl en dioxano (0,5 ml, 2 mmol) que se agitó a temperatura ambiente durante 15 h. La solución se extrajo tres veces con agua. Las fracciones acuosas se combinaron y se concentraron para producir la sal di-HCl del compuesto del título en forma de un sólido de color blanco (26 mg, 0,06 mmol, 32%): LC-MS (ES) m/z 341 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,49 (s a, 3 H) 3,43 (d, *J* = 4,80 Hz, 1 H) 3,55 (d, *J* = 10,36 Hz, 1 H) 3,95 (s, 3 H) 5,41-5,43 (m, 1 H) 6,66 (d, *J* = 2,27 Hz, 1 H) 7,38 (d, *J* = 7,07 Hz, 1 H) 7,44 (t, *J* = 7,33 Hz, 2 H) 7,48 - 7,53 (m, 2 H) 7,94 - 8,02 (m, 2 H).

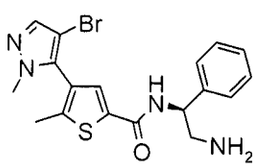
Ejemplo 199



Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 24, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (89 mg, 0,4 mmol) [preparado de acuerdo con el Ejemplo 198] y se sustituyó (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo (94 mg, 0,4 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1]: LC-MS (ES) m/z 375 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,38-2,41 (m, 1H), 3,38 (d, *J* = 1,52 Hz, 1 H) 3,49 (d, *J* = 10,86 Hz, 1 H) 3,73 (s a, 3 H) 5,41 (d, *J* = 3,54 Hz, 1 H) 7,30 - 7,50 (m, 5 H) 7,54 - 7,62 (m, 1 H) 7,81 (s a, 1 H).

Ejemplo 200

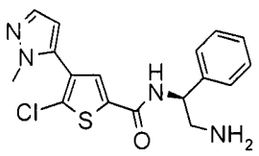


Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 24, con la excepción de que se sustituyó ácido 4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico por ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (168 mg, 0,5 mmol) [preparado de acuerdo con el Ejemplo 198], N-clorosuccinimida por N-bromosuccinimida (88,5 mg, 0,5 mmol) y (3-amino-4-fenilbutil)carbamato de 1,1-dimetiletilo por (2-amino-3-

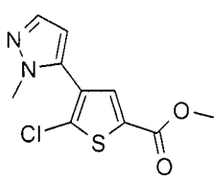
fenilpropil)carbamato de 1,1-dimetiletilo (71 mg, 0,3 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1]: LC-MS (ES) m/z 341 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 2,39 (d, *J* = 4,04 Hz, 3 H) 3,42 (s a, 1 H) 3,55 (s a, 1 H) 3,75-3,78 (m, 3 H) 5,45 (m, 1 H) 7,37 (d, *J* = 7,07 Hz, 1 H) 7,40 - 7,46 (m, 2 H) 7,49 (s a, 2 H) 7,59 - 7,68 (m, 1 H) 7,80 - 7,88 (m, 1 H).

Ejemplo 201



Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una solución de 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (2,56 g, 10,00 mmol) [preparado de acuerdo con el Ejemplo 95], 5-(5,5-dimetil)-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (3,88 g, 20,0 mmol) [preparado de acuerdo con la Preparación 7], carbonato potásico (4,15 g, 30,0 mmol) y complejo de 1,1'-bis(difenilfosfino)ferrocenodicloro paladio (II) y diclorometano (0,073 g, 0,1 mmol) en 1,4-dioxano (12 ml) y agua (3,00 ml) se calentaron a 80°C en un tubo cerrado herméticamente. Después de 3 h, se añadió otra extracción de 5-(5,5-dimetil)-1,3,2-dioxaborinan-2-il)-1-metil-1H-pirazol (1,94 g, 10,0 mmol) y complejo de 1,1'-bis(difenilfosfino)ferrocenodicloro paladio (II) y diclorometano (0,073 g, 0,1 mmol). Después de 2 h, la mezcla se concentró y se purificó por gel de sílice eluyendo con acetato de etilo al 0-35%/hexano produciendo el compuesto del título en forma de un sólido de color amarillo (1,74 g, 3,35 mmol, 34%): LC-MS (ES) m/z 257 $(M+H)^+$.

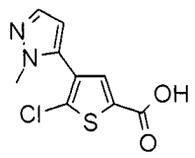
b) ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico

Organizacion y
Digitalizacion CSA Ltda

PATENTE DE INVENCIÓN

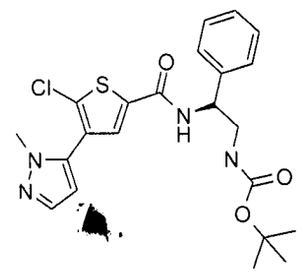
09-82387

5/5



Una solución de 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (304 mg, 1,18 mmol) en hidróxido sódico 6 N (2 ml, 12 mmol) y tetrahidrofurano (10 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~3 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo el producto deseado (276 mg, 1,14 mmol, rendimiento de 96%) en forma de un aceite de color amarillo: LC-MS (ES) m/e 244 $(M+H)^+$.

c) [(2*S*)-2-({[5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo

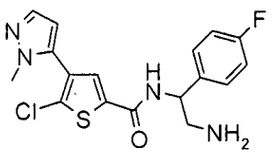


A una solución de ácido 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (60 mg, 0,25 mmol), [(2*S*)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo (58 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1] y diisopropiletilamina (0,12 ml, 0,75 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (190 mg, 0,41 mmol). La solución se agitó a 25°C durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo el compuesto del título (90 mg, 0,20 mmol, rendimiento de 79%) en forma de un aceite incoloro: LC-MS (ES) m/e 461 (M+H)+.

d) *N*-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A una solución de [(2*S*)-2-({[5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo (90 mg, 0,20 mmol) en DCM (2 ml) se le añadió una solución 4 N de HCl en dioxano (0,5 ml, 2 mmol). Después de 15 h, la solución se extrajo tres veces con agua. Las fracciones acuosas se combinaron y se concentraron para producir la sal di-HCl del compuesto del título en forma de un sólido de color blanco (63 mg, 0,14 mmol, 74%): : LC-MS (ES) m/z 361 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,41 (dd, *J* = 13,01, 4,17 Hz, 1 H) 3,63 (d, *J* = 10,86 Hz, 1 H) 4,08 (s, 3 H) 5,45 (dd, *J* = 10,48, 4,17 Hz, 1 H) 6,87 (d, *J* = 2,27 Hz, 1 H) 7,36 (d, *J* = 7,33 Hz, 1 H) 7,42 (t, *J* = 7,33 Hz, 2 H) 7,54 (d, *J* = 7,07 Hz, 2 H) 8,14 (d, *J* = 2,27 Hz, 1 H) 8,27 (s, 1 H).

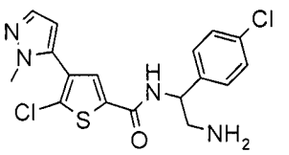
Ejemplo 202



Preparación de *N*-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 201, con la excepción de que se sustituyó [(2S)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo por [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo (63 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z = 379 $(M+H)^+$, ^{1}H RMN (CD_3OD, 400 MHz) ppm 3,40 (dd, *J* = 13,01, 4,42 Hz, 1 H) 3,66 (d, *J* = 2,02 Hz, 1 H) 4,03 - 4,15 (m, 3 H) 5,46 (dd, *J* = 10,36, 4,29 Hz, 1 H) 6,84 (d, *J* = 2,53 Hz, 1H) 7,15 (t, *J* = 8,72 Hz, 2 H) 7,60 (dd, *J* = 8,59, 5,05 Hz, 2 H) 8,10 (d, *J* = 2,53 Hz, 1 H) 8,29 (s, 1 H).

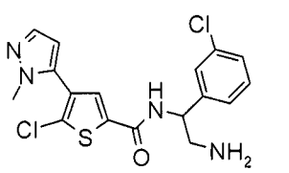
Ejemplo 203



Preparación de *N*-[2-amino-1-(4-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 201, con la excepción de que se sustituyó [(2S)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo por [2-amino-2-(4-clorofenil)etil]carbamato de 1,1-dimetiletilo (45 mg, 0,17 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z = 396 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) ppm 3,40 (d, *J* = 4,55 Hz, 1 H) 3,58 (d, *J* = 10,36 Hz, 1 H) 3,98 (s, 3 H) 5,41 (d, *J* = 4,55 Hz, 1 H) 6,71 (s, 1 H) 7,43 (dt, *J* = 4,74, 2,31 Hz, 2 H) 7,47 - 7,56 (m, 2 H) 7,92 (s a, 1 H) 8,13 (s, 1 H).

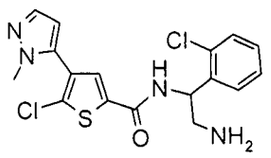
Ejemplo 204



Preparación de *N*-[2-amino-1-(3-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 201, con la excepción de que se sustituyó [(2S)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo por [2-amino-2-(3-clorofenil)etil]carbamato de 1,1-dimetiletilo (67 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z = 396 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) ppm 3,41 (dd, *J* = 12,76, 4,93 Hz, 5 H) 3,36 - 3,47 (m, 3 H) 3,63 (s, 2 H) 3,59 (d, *J* = 10,61 Hz, 6 H) 3,95 (s, 9 H) 4,02 (d, *J* = 3,03 Hz, 15 H) 5,41 (dd, *J* = 9,09, 3,79 Hz, 8 H) 6,67 (d, *J* = 2,27 Hz, 3 H) 6,78 (s a, 4 H) 7,33 - 7,49 (m, 23 H) 7,56 (s a, 7 H) 8,06 (s a, 8 H) 8,16 (d, *J* = 16,93 Hz, 6 H).

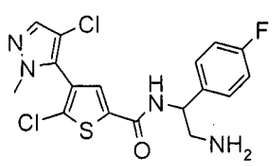
Ejemplo 205



Preparación de *N*-[2-amino-1-(2-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

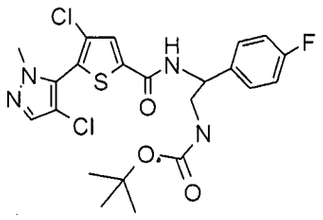
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 201, con la excepción de que se sustituyó [(2S)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo por [2-amino-2-(2-clorofenil)etil]carbamato de 1,1-dimetiletilo (67 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z = 396 $(M+H)^+$, ^{1}H RMN (CD_3OD, 400 MHz) ppm 3,39 (s a, 1 H) 3,56 (d, *J* = 10,86 Hz, 1 H) 4,05 (d, *J* = 3,03 Hz, 3 H) 5,87 (dd, *J* = 10,74, 3,41 Hz, 1 H) 6,81 (s a, 1 H) 7,39 (s a, 2 H) 7,50 (d, *J* = 6,57 Hz, 1 H) 7,70 (d, *J* = 7,07 Hz, 1 H) 8,04 (s a, 1 H) 8,26 (s a, 1 H).

Ejemplo 206



Preparación de *N*-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

a) [2-({[4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo

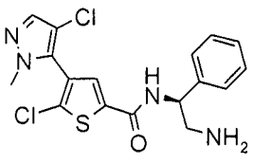


A una solución de ácido 4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (67 mg, 0,24 mmol) [preparado de acuerdo con el Ejemplo 193], [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo (61 mg, 0,24 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16] y diisopropiletil amina (126 µl, 0,72 mmol) en DCM (5 ml) se le añadió en una porción PyBrop (168 mg, 0,36 mmol). Después de 1 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, gradiente de acetato de etilo al 0- 50%/hexano), produciendo el compuesto del título (93 mg, 0,18 mmol, 76%) en forma de un sólido de color blanco: LCMS (ES) m/z = 514 $(M+H)^+$.

b). *N*-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida

A una solución de [2-({[4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo (90 mg, 0,17 mmol) en DCM (2 ml) se le añadió una solución 4 N de HCl en dioxano (0,43 ml, 1,75 mmol). Después de 15 h, la solución se extrajo tres veces con agua. Las fracciones acuosas se combinaron y se concentraron para producir la sal di-HCl del compuesto del título en forma de un sólido de color blanco (39,6 mg, 0,09 mmol, 52%): LC-MS (ES) m/z 414 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,42 (d, *J* = 2,78 Hz, 1 H) 3,56 (s a, 1 H) 3,79 (s, 3 H) 5,43 (dd, *J* = 10,23, 4,67 Hz, 1 H) 7,11 - 7,22 (m, 2 H) 7,49 - 7,57 (m, 2 H) 7,60 (s, 1 H) 7,93 (s a, 1 H).

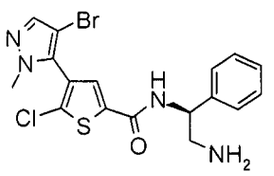
Ejemplo 207



Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

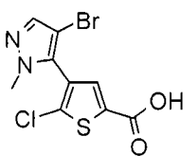
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 206, con la excepción de que se sustituyó [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo por [(2S)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo (57 mg, 0,24 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1]: LC-MS (ES) m/z 396 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 3,42 (s a, 1 H) 3,57 (d, *J* = 11,12 Hz, 1H) 3,80 (s, 3 H) 5,44 (dd, *J* = 10,36, 4,29 Hz, 1 H) 7,37 (d, *J* = 2,53 Hz, 1 H) 7,40 - 7,47 (m, 2 H) 7,48 - 7,55 (m, 2 H) 7,60 (s, 1 H) 7,95 (s a, 1 H).

Ejemplo 208



Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

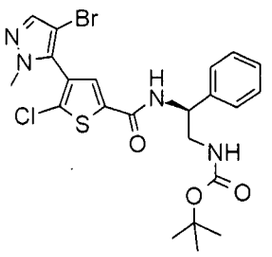
a) ácido 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxílico



A una solución de 5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (300 mg, 1,169 mmol) [preparado de acuerdo con el procedimiento del Ejemplo 193] en THF (10 ml) se le añadió *N*-bromosuccinimida (212 mg, 1,19 mmol). La mezcla se cerró herméticamente y se calentó a 70°C. Después de 2 h,

se añadió en una porción una solución de NaOH 6 N (2,0 ml, 6,0 M, 11,84 mmol). La mezcla resultante se agitó durante 2 h más y se repartió entre DCM-H_2O. El valor del pH de la fase acuosa se ajustó a ~3 y se extrajo varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo el compuesto del título en forma de un aceite incoloro (105 mg, 28%): LC-MS (ES) m/z = 322 $(M+H)^+$.

b) [(2*S*)-2-({[4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo



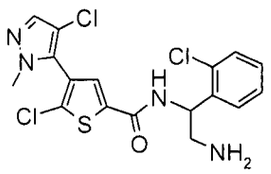
A una solución de ácido 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxílico (80 mg, 0,25 mmol), [(2S)-2-amino-2-feniletil]carbamato de 1,1-dimetiletilo (59 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 1] y diisopropiletil amina (128 µl, 0,75 mmol) en DCM (5 ml) se le añadió en una porción PyBrop (168 mg, 0,36 mmol). Después de 3 h, los contenidos de la reacción se repartieron entre H_2O/DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, gradiente de acetato de etilo al 0- 50%/hexano), produciendo el compuesto del título (110 mg, 0,18 mmol, 73%) en forma de un sólido de color blanco: LCMS (ES) m/z = 540 $(M+H)^+$.

c). *N*-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida

A una solución de [(2*S*)-2-({[4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo (81 mg, 0,15 mmol) en DCM (2 ml) se le añadió una solución 4 N de HCl en dioxano (0,38 ml, 1,5 mmol).

Después de 15 h, la solución se extrajo tres veces con agua. Las fracciones acuosas se combinaron y se concentraron para producir la sal di-HCl del compuesto del título en forma de un sólido de color blanco (18,3 mg, 0,04 mmol, 26%): LC-MS (ES) m/z 440 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,40 (d, *J* = 13,89 Hz, 1H) 3,60 (s a, 1 H) 3,80 (s a, 3 H) 5,38 - 5,50 (m, 1 H) 7,37 (d, *J* = 7,33 Hz, 1 H) 7,43 (t, *J* = 7,45 Hz, 2 H) 7,52 (d, *J* = 7,58 Hz, 2 H) 7,61 (s, 1 H) 8,02 (s a, 1 H)

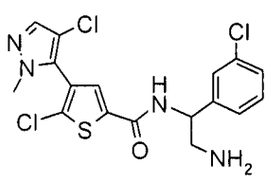
Ejemplo 209



Preparación de *N*-[2-amino-1-(2-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 206, con la excepción de que se sustituyó [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo por [2-amino-2-(3-clorofenil)etil]carbamato de 1,1-dimetiletilo (67 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z 430 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,45 (d, *J* = 5,56 Hz, 2 H) 3,72 - 3,81 (m, 3 H) 5,86 (dd, *J* = 9,22, 4,42 Hz, 1H) 7,41 (d, *J* = 2,02 Hz, 2 H) 7,48 - 7,55 (m, 1 H) 7,58 (s a, 2 H) 7,83 (s, 1 H)

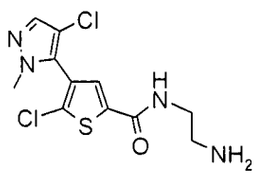
Ejemplo 210



Preparación de *N*-[2-amino-1-(3-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 206, con la excepción de que se sustituyó [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo por [2-amino-2-(3-clorofenil)etil]carbamato de 1,1-dimetiletilo (67 mg, 0,25 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z 430 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,44 (d, *J* = 3,54 Hz, 1 H) 3,55 (d, *J* = 10,61 Hz, 1 H) 3,80 (s, 3 H) 5,42 (dd, *J* = 10,36, 4,29 Hz, 1 H) 7,35 - 7,49 (m, 3 H) 7,55 (s, 1 H) 7,59 (s, 1 H) 7,95 (d, *J* = 14,40 Hz, 1 H)

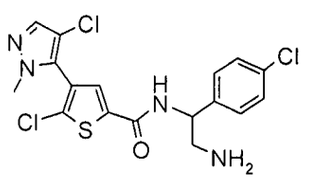
Ejemplo 211



Preparación de *N*-(2-aminoetil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 206, con la excepción de que se sustituyó [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo por (2-aminoetil)carbamato de 1,1-dimetiletilo (58 mg, 0,36 mmol): LC-MS (ES) m/z 320 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,17 (d, *J* = 5,81 Hz, 2 H) 3,66 (s a, 2 H) 3,78 (s, 3 H) 7,60 (s, 1 H) 7,66 (s, 1H)

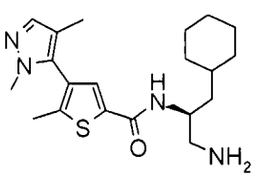
Ejemplo 212



Preparación de *N*-[2-amino-1-(4-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 206, con la excepción de que se sustituyó [2-amino-2-(4-fluorofenil)etil]carbamato de 1,1-dimetiletilo por [2-amino-2-(4-clorofenil)etil]carbamato de 1,1-dimetiletilo (65 mg, 0,24 mmol) [preparado de acuerdo con el procedimiento de la Preparación 16]: LC-MS (ES) m/z 431 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 3,43 (d, *J* = 4,55 Hz, 1 H) 3,53 (d, *J* = 10,11 Hz, 1 H) 3,79 (s, 3 H) 5,43 (dd, *J* = 10,36, 4,55 Hz, 1H) 7,43 - 7,47 (m, 2 H) 7,48 - 7,53 (m, 2 H) 7,60 (s, 1 H) 7,94 (s,1 H)

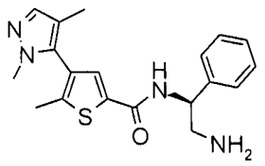
Ejemplo 213



Preparación de *N*-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

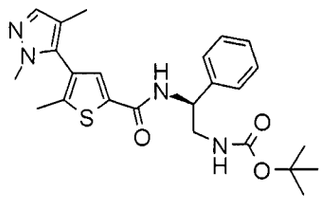
El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 99, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona (73 mg, 0,25 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 375 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 0,91- 0,99 (m, 1H), 1,01-1,10 (m., 1 H) 1,39-1,47 (m., 3 H) 1,37-1,48 (m, 2 H) 1,65 - 1,77 (m, 5 H) 1,89 (s a, 1 H) 2,10 (s, 3 H) 2,45 (s, 3 H) 3,07 - 3,16 (m, 2 H) 3,91 - 3,98 (m, 3 H) 4,42 (s a, 1 H) 7,91 (s a, 1 H) 8,24 (s, 1 H)

Ejemplo 214



Preparación de *N*-[(1*S*)-2-amino-1-feniletil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

a) [(2*S*)-2-({[4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo



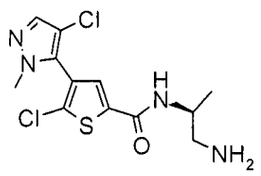
A una solución de ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (110 mg, 0,4 mmol) [preparado en el Experimento 99], 2-[(2S)-2-amino-4-metilpentil]-1H-isoindolo-1,3(2H)-diona (99 mg, 0,4 mmol) [preparada de acuerdo con el procedimiento de la Preparación 1] y diisopropiletilamina (0,2 ml, 1,2 mmol) en DCM a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (280 mg, 0,6 mmol). La solución se agitó a 25°C durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo el compuesto del título (113 mg, 0,22 mmol, rendimiento de 56%) en forma de un aceite incoloro: LC-MS (ES) m/e 506 (M+H)+.

d) *N*-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

A una solución de [(2*S*)-2-({[4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tienil]carbonil}amino)-2-feniletil]carbamato de 1,1-dimetiletilo (99 mg, 0,22 mmol) en DCM (2 ml) se le añadió una solución 4 N de HCl en dioxano (0,5 ml, 2 mmol). Después de 15 h, la solución se extrajo tres veces con agua. Las fracciones acuosas se combinaron y se concentraron para producir la sal di-HCl del

compuesto del título en forma de un sólido de color blanquecino (40 mg, 0,11 mmol, 52%): LC-MS (ES) m/z 355 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 1,99 - 2,14 (m, 3 H) 2,43 (s, 3 H) 3,39 (d, *J* = 9,85 Hz, 1 H)) 3,60 (d, *J* = 9,85 Hz, 1 H) 3,92 (s a, 3 H) 5,44 (d, *J* = 8,84 Hz, 1 H) 7,36 (d, *J* = 2,53 Hz, 1 H) 7,43 (t, *J* = 5,94 Hz, 2 H) 7,49 - 7,57 (m, 2 H) 8,03 (s a, 1 H) 8,14 (s a, 1H).

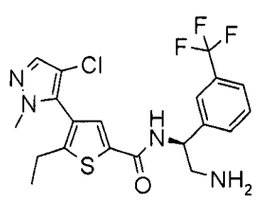
Ejemplo 215



Preparación de *N*-[(1*S*)-2-amino-1-metiletil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 106, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-aminopropil]-1H-isoindolo-1,3(2H)-diona (74 mg, 0,36 mmol): LC-MS (ES) m/z 333 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 1,37 (d, *J* = 6,82 Hz, 3 H) 3,11 - 3,14 (m, 2 H) 3,79 (s, 3 H) 4,38 – 4,40 (m, 1 H) 7,60 (s a, 1 H) 7,83 (d, *J* = 2,27 Hz, 1 H).

Ejemplo 216

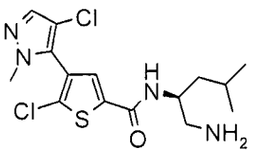


Preparación de *N*-{(1*S*)-2-amino-1-[3-(trifluorometil)fenil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 100, con la excepción de

que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (348 mg, 1,0 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 471 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 1,24 (t, *J* = 7,33 Hz, 3 H) 2,54 (d, *J* = 8,84 Hz, 2 H) 2,74 (c, *J* = 7,24 Hz, 2 H) 3,05 - 3,16 (m, 1 H) 3,26 (d, *J* = 4,80 Hz, 1 H) 3,66 - 3,79 (m, 3 H) 4,54 (s a, 1 H) 7,47 - 7,56 (m, 2 H) 7,57 - 7,76 (m, 4 H).

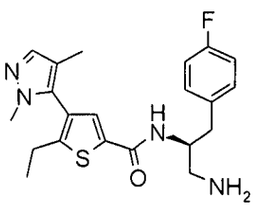
Ejemplo 217



Preparación de *N*-[(1*S*)-1-(aminometil)-3-metilbutil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

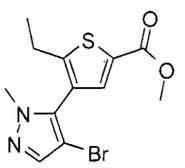
El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 106, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-4-metilpentil]-1H-isoindolo-1,3(2H)-diona (99 mg, 0,4 mmol): LC-MS (ES) m/z 376 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 0,99 (t, *J* = 6,44 Hz, 6 H) 1,42 (s, 1 H) 1,63 - 1,80 (m, 2 H) 3,04 (s a, 1 H) 3,14 (d, *J* = 3,54 Hz, 1 H) 3,80 (s, 3 H) 4,42 (s a, 1 H) 7,59 (s, 1 H) 7,84 (d, *J* = 6,06 Hz, 1 H).

Experimento 218



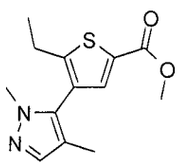
Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida

a) 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo



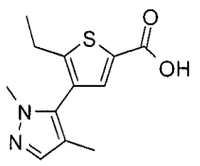
A una solución de 5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (600 mg, 2,40 mmol) [preparado de acuerdo con el Ejemplo 98] en tetrahidrofurano (THF) (10 ml) se le añadió N-bromosuccinimida (512 mg, 2,88 mmol). La mezcla se agitó en un tubo cerrado herméticamente a 70°C durante 2 h. Después, la mezcla de reacción se concentró y se purificó con gel de sílice usando un gradiente al 0-5% de (acetato de etilo/hexano) para producir el compuesto del título en forma de un sólido de color blanquecino: LC-MS (ES) m/z 330 $(M+H)^+$.

b) 4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo



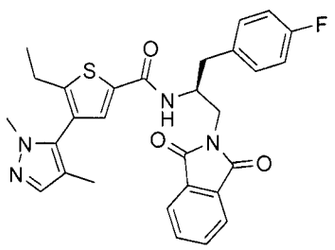
Una solución de 4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metilo (635 mg, 1,93 mmol), carbonato potásico (1,33 g, 9,64 mmol), $PdCl_2$(dppf) (141 mg, 0,19 mmol) y trimetilboroxina (0,54 ml, 3,86 mmol) en N,N-dimetilformamida (3 ml) se agitó a 110°C en un tubo cerrado herméticamente durante 2 h. Esta mezcla de reacción se concentró y se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 10-50% en hexanos), produciendo el compuesto del título (488 mg, 96%) en forma de un aceite de color amarillo: LCMS (ES) m/e 265 (M+H)+.

c) ácido 4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxílico



Una solución de 4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxilato de metil o 488 mg, 1,85 mmol) en hidróxido sódico 6 N (3,08 ml, 18,5 mmol) y tetrahidrofurano (10 ml) se agitó a 70ºC en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo el compuesto del título en forma de una espuma amarilla (448 mg, 1,79 mmol, rendimiento de 96%) en forma de un aceite de color amarillo: LCMS (ES) m/e 251 (M+H)+.

d) 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-etil-2-tiofenocarboxamida

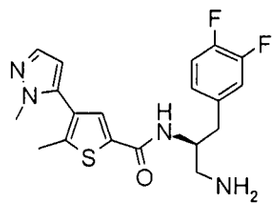


A una solución de ácido 4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxílico (250 mg, 1,0 mmol), 2-{(2S)-2-amino-3-[4-(fluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (313 mg, 1,05 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y diisopropiletilamina (0,52 ml, 3 mmol) en DCM a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (746 mg, 1,6 mmol). La solución se agitó a 25ºC durante 12 h y después se repartió entre H_2O y DCM. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (sílice, EtOAc al 30-70% en hexanos), produciendo el compuesto del título en forma de un sólido de color amarillo (490 mg, 0,92 mmol, rendimiento de 92%) en forma de una espuma amarilla: LCMS (ES) m/e 531 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida

A una solución de 4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(4-fluorofenil)metil]etil}-5-etil-2-tiofenocarboxamida (400 mg, 0,75 mmol) en metanol (8 ml) a 25ºC se le añadió gota a gota hidrazina (0,12 ml, 3,77 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se transfirió a la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl del compuesto del título en forma de un sólido de color amarillo: LC-MS (ES) m/z 401 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 1,28 (t, *J* = 7,58 Hz, 3 H) 2,07 (s, 3 H) 2,75 (m, 2 H) 3,02 (d, *J* = 6,32 Hz, 2 H) 3,22 (s a, 2 H) 3,92 (d, *J* = 2,27 Hz, 3 H) 4,53 (s a, 1 H) 7,02 (t, *J* = 8,59 Hz, 2 H) 7,34 (m, 2H), 7,80 (s, 1 H) 8,13 - 8,25 (m, 1 H).

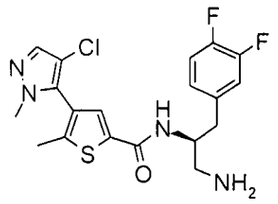
Ejemplo 219



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 103, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (332 mg, 1,05 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 391 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,44 (s, 3 H) 2,91 - 3,02 (m, 2 H) 3,16 (d, *J* = 10,11 Hz, 1 H) 3,24 (dd, *J* = 13,14, 3,54 Hz, 1H) 3,82 (s, 3 H) 4,50 (d, *J* = 3,54 Hz, 1 H) 6,44 (d, *J* = 2,02 Hz, 1H) 7,05 - 7,13 (m, 1 H)7,15-7,25 (m, 2H), 7,67-7,70 (m, 2 H).

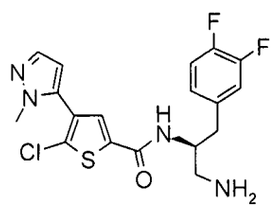
Ejemplo 220



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 102, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (332 mg, 1,05 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 425 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,40 (s, 3 H) 2,95 - 3,03 (m, 2 H) 3,23 - 3,26 (m, 2 H) 3,76 (s a, 3H) 4,96 - 4,52 (m, 1H), 7,07 - 7,15 (m, 2H) 7,22 - 7,28 (m, 1H) 7,55 - 7,77 (m, 2H).

Ejemplo 221

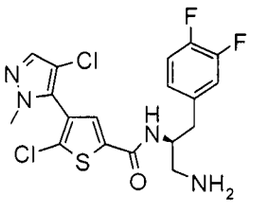


Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 104, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (332 mg, 1,05 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z

411 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 3,02 (d, *J* = 7,33 Hz, 2 H) 3,24 (d, *J* = 6,82 Hz, 2 H) 4,01 (d, *J* = 7,58 Hz, 3 H) 4,52 (d, *J* = 7,07 Hz, 1 H) 6,78 (d, *J* = 11,87 Hz, 1 H) 7,08 - 7,21 (m, 1 H) 7,26 - 7,28 (m, 1 H) 7,94 - 8,08 (m, 2 H).

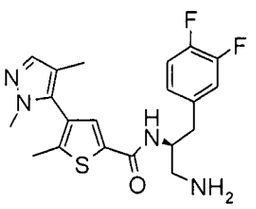
Ejemplo 222



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 106, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-ciclohexilpropil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (332 mg, 1,05 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 446 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 2,95 - 3,05 (m, 2 H) 3,22 - 3,23 (m, 2 H) 3,79 (s, 3 H) 4,52 (s a, 1 H) 7,08 - 7,21 (m, 2 H) 7,27 - 7,26 (m, 2 H) 7,60 (s, 1 H) 7,83 (s a, 1 H).

Ejemplo 223

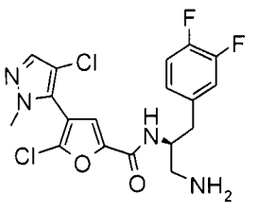


Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 99, con la excepción de que se

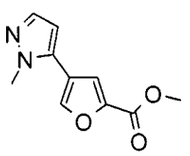
sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (332 mg, 1,05 mmol) [preparada de acuerdo con la Preparación 6]: LC-MS (ES) m/z 405 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 2,09 (s, 15 H) 2,42 (s, 3 H) 3,04 (d, *J* = 7,07 Hz, 2 H) 3,27 (d, *J* = 4,80 Hz, 2 H) 3,88 - 4,01 (m, 3H) 4,54 (s a, 1 H) 7,08 - 7,21 (m, 2 H) 7,29 (d, *J* = 7,58 Hz, 1 H) 7,92 (s a, 1H) 8,15 - 8,26 (m, 1 H).

Ejemplo 224



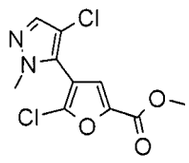
Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

a) 4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



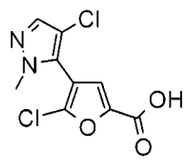
Una solución de 4-bromo-2-furanocarboxilato de metilo (470 mg, 2,29 mmol), carbonato potásico (1584 mg, 11,46 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (525 mg, 2,52 mmol) [preparado de acuerdo con la Preparación 7] y bis-(tri-t-butilfosfina)paladio (0) (58,6 mg, 0,12 mmol) en 1,4-dioxano (9,55 ml) y agua (1,9 ml) se agitó a 80ºC. Después de 1 h, la solución se repartió entre H_2O y DCM y la fase acuosa se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y se purificaron por cromatografía en columna (EtOAc al 30% en hexanos), produciendo el compuesto del título (124 mg, 0,60 mmol, rendimiento de 26%) en forma de un polvo de color blanco: LCMS (ES) m/e 206 $(M+H)^+$.

b) 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo



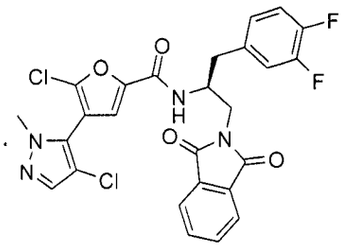
Una solución de 4-(1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (412 mg, 2,0 mmol) y N-clorosuccinimida (267 mg, 2,0 mmol) en DMF (10 ml) se calentó a 75°C durante 30 minutos. Se añadió otra extracción de N-clorosuccinimida (267 mg, 2,0 mmol). Después de 1 h, la mezcla se concentró y se purificó usando gel de sílice y eluyendo con acetato de etilo al 0-55%/hexano para producir el compuesto del título en forma de un sólido de color blanco (225 mg, 0,82 mmol, rendimiento de 71%): LCMS (ES) m/e 276 $(M+H)^+$.

c) ácido 5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxílico



Una solución de 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (224 mg, 0,82 mmol) en hidróxido sódico 6 N (1,36 ml, 8,2 mmol) y tetrahidrofurano (5 ml) se agitó a 70°C en un tubo cerrado herméticamente durante 1 h. La solución resultante se enfrió y después se repartió entre H_2O y DCM. La fase acuosa se ajustó a un valor de pH de ~4 y después se lavó varias veces con DCM. Las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo el compuesto del título (201 mg, 0,77 mmol, rendimiento de 94%) en forma de un aceite de color amarillo: LCMS (ES) m/e 262 $(M+H)^+$.

d) 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-furanocarboxamida

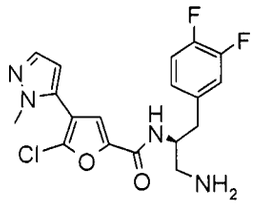


A una solución de ácido 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxílico (200 mg, 0,77 mmol) [preparado de acuerdo con el procedimiento de la Preparación 6], 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (254 mg, 0,80 mmol) y N,N-diisopropiletilamina (0,40 ml, 2,30 mmol) en DCM (10 ml) se le añadió hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (536 mg, 1,15 mmol). Después de agitar a temperatura ambiente durante 20 h, la mezcla se concentró y se purificó con una columna de gel de sílice eluyendo con un gradiente de (acetato de etilo al 0-50%/hexanos) para producir el compuesto del título en forma de un sólido espumoso de color blanquecino (304 mg, 0,54 mmol, rendimiento de 71%): LCMS (ES) m/e 560 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

A una solución de 5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-N-{(1S)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-2-furanocarboxamida (304 mg, 0,54 mmol) en metanol (5 ml) a 25ºC se le añadió gota a gota hidrazina (0,08 ml, 2,7 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl del compuesto del título en forma de un sólido de color amarillo: LC-MS (ES) m/z 430 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,91 - 3,05 (m, 2 H) 3,17 - 3,28 (m, 2 H) 3,81 (s, 3 H) 4,57 (d, *J* = 9,60 Hz, 1 H) 7,12 (s a, 1 H) 7,18-7,28 (m., 2 H) 7,36-7,39 (m, 1 H) 7,58 (s, 1 H).

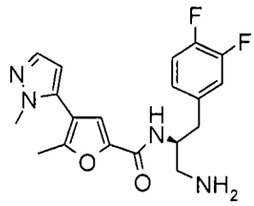
Ejemplo 225



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

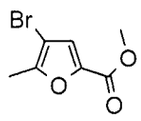
El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 127, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (147 mg, 0,46 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 395 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,90 - 3,06 (m, 2 H) 3,18-3,24 (m, 2 H) 3,98 (d, *J* = 17,68 Hz, 3 H) 4,52 - 4,64 (m, 1 H) 6,67 (d, *J* = 1,77 Hz, 1 H) 7,19 (dd, *J* = 10,11, 8,59 Hz, 2 H) 7,26 (td, *J* = 9,73, 2,27 Hz, 1 H) 7,51 (d, *J* = 19,96 Hz, 1 H) 7,93 (s a, 1 H).

Ejemplo 226



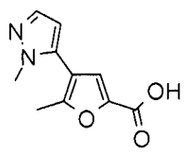
Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

a) 4-bromo-5-metil-2-furanocarboxilato de metilo



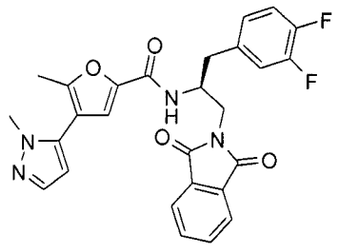
Se combinaron 4,5-dibromo-2-furanocarboxilato de metilo (3,7 g, 13,03 mmol) [preparado de acuerdo con el Ejemplo 127] y trans-diclorobis(trifenilfosfina)paladio (II) (0,46 g, 0,65 mmol) en THF (50 ml) para dar una suspensión de color amarillo. Se añadió gota a gota una solución en THF de cloruro de metilcinc (11,40 ml, 22,81 mmol) a temperatura ambiente. Después de agitar a temperatura ambiente durante 20 h, la solución se concentró y se purificó usando gel de sílice y eluyendo con acetato de etilo al 0-30%/hexano para generar el compuesto del título en forma de un sólido de color blanco (1,45 g, 6,61 mmol, rendimiento de 51%): LC-MS (ES) m/z 220 $(M+H)^+$.

b) ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxílico



A una solución de 4-bromo-5-metil-2-furanocarboxilato de metilo (500 mg, 2,28 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (950 mg, 4,57 mmol) [preparado de acuerdo con la Preparación 7] y carbonato potásico (315 mg, 2,28 mmol) en 1,4-dioxano (8 ml) y agua (2,0 ml) se le añadió bis(tri-t-butilfosfina)paladio (0) (117 mg, 0,23 mmol). La mezcla se calentó a 80°C y después de 15 h, la mezcla de reacción se concentró. El residuo se repartió entre DCM y agua. La capa orgánica se concentró y se disolvió en tetrahidrofurano (THF) (8,0 ml). La solución se trató con una solución acuosa 6 N de hidróxido sódico (3,80 ml, 22,83 mmol) y se calentó a 75°C. Después de 15 h, la mezcla de reacción se concentró y se repartió entre DCM y agua. La capa acuosa se acidificó a un valor de pH de ~3 con una solución acuosa 2 N de HCl y se extrajo varias veces con DCM. Las fracciones orgánicas se combinaron y se concentraron para producir el compuesto del título en forma de un sólido de color amarillo (401 mg, 1,95 mmol, rendimiento de 85%): LC-MS (ES) m/z 207 $(M+H)^+$.

c) *N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

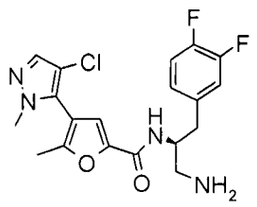


A una solución de ácido 5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxílico (200 mg, 0,97 mmol), 2-[(2S)-2-amino-3-(2,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (322 mg, 1,02 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y N,N-diisopropiletilamina (0,51 ml, 2,91 mmol) en DCM (10 ml) se le añadió hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (678 mg, 1,46 mmol). Después de agitar a temperatura ambiente durante 20 h, la mezcla se concentró y se purificó usando gel de sílice y eluyendo con un gradiente de acetato de etilo al 0-50%/hexano para producir el compuesto del título en forma de un sólido espumoso de color blanquecino (181 mg, 0,36 mmol, rendimiento de 37%): LCMS (ES) m/e 505 (M+H)+.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida

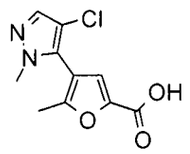
A una solución de *N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida (176 mg, 0,35 mmol) en metanol (5 ml) a 25°C se le añadió gota a gota hidrazina (0,22 ml, 0,7 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl del compuesto del título en forma de un sólido de color blanquecino: LC-MS (ES) m/z 430 $(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,91 - 3,05 (m, 2 H) 3,17 - 3,28 (m, 2 H) 3,81 (s, 3 H) 4,57 (d, *J* = 9,60 Hz, 1 H) 7,12 (s a, 1 H) 7,18-7,28 (m., 2 H) 7,36-7,39 (m, 1 H) 7,58 (s, 1 H)

Ejemplo 227



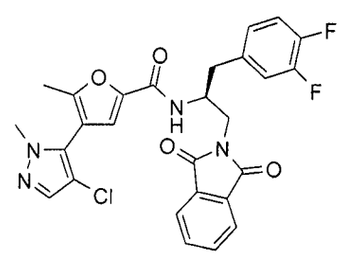
Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

a) ácido 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxílico



A una solución de ácido 5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxílico (150 mg, 0,73 mmol) [preparado en el Ejemplo 126] en THF (10 ml) se le añadió N-clorosuccinimida (97 mg, 0,73 mmol). Después de agitar a 70ºC durante 20 h en un tubo cerrado herméticamente, la mezcla se repartió entre H_2O y DCM y el valor del pH de la fase acuosa se ajustó a ~4. La fase acuosa se lavó varias veces con DCM y las fracciones orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron, produciendo el compuesto del título en forma de un sólido espumoso de color blanquecino (152 mg, 0,63 mmol, rendimiento de 87%): LC-MS (ES) m/z 241 $(M+H)^+$.

b) 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-2-furanocarboxamida



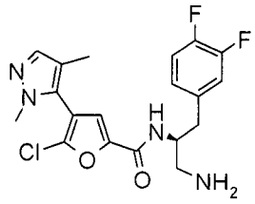
A una solución de ácido 4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxílico (150 mg, 0,62 mmol), 2-[(2S)-2-amino-3-(3,4-difluorofenil)propil]-

1H-isoindolo-1,3(2H)-diona (207 mg, 0,65 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6] y N,N-diisopropiletil amina (0,33 ml, 1,87 mmol) en DCM (10 ml) se le añadió hexafluorofosfato de bromo-tris-pirrolidino-fosfonio (436 mg, 0,94 mmol). Después de agitar a temperatura ambiente durante 20 h, la mezcla se concentró y se purificó usando gel de sílice y eluyendo con un gradiente de acetato de etilo al 0-50%/hexano para producir el compuesto del título en forma de una espuma de color blanquecino (200 mg, 0,35 mmol, rendimiento de 57%): LC-MS (ES) m/z 539 $(M+H)^+$.

c) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

A una solución de 4-(4-cloro-1-metil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-2-furanocarboxamida (210 mg, 0,39 mmol) en metanol (5 ml) a 25ºC se le añadió gota a gota hidrazina (0,02 ml, 0,78 mmol). Después de 12 h, la solución se concentró, se cargó en seco sobre sílice y se purificó por cromatografía en columna (MeOH al 5% en DCM (NH_4OH al 1%)). La base libre se convirtió en la sal HCl mediante la adición al residuo de un exceso de HCl 4 M en dioxano (1 ml) en MeOH (2 ml), produciendo la sal HCl del compuesto del título en forma de un sólido de color blanquecino: LC-MS (ES) m/z 409$(M+H)^+$, ^{1}H RMN (400 MHz, MeOD) δ ppm 2,38 (s, 3 H) 2,98 (d, *J* = 9,35 Hz, 1 H) 3,01 (d, *J* = 5,56 Hz, 1 H) 3,23 (dd, *J* = 13,01, 8,97 Hz, 2 H) 3,73 - 3,83 (m, 3 H) 4,56 (d, *J* = 9,35 Hz, 1H) 7,17 (s, 1 H) 7,18 - 7,32 (m, 3 H) 7,57 (s, 1 H).

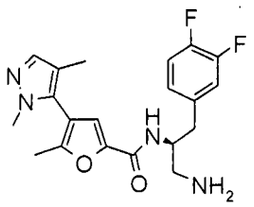
Ejemplo 228



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 118, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (253 mg, 0,8 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 409 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 2,05 - 2,15 (m, 3H) 2,91 - 3,07 (m, 2 H) 3,16 - 3,26 m., 2 H) 3,91 (s a, 3 H) 4,57 - 4,59 (m., 1 H) 7,09 - 7,31 (m, 3 H) 7,51 (s a, 1 H) 8,07 (s a, 1 H)

Ejemplo 229

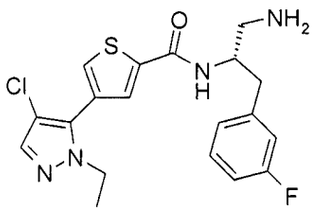


Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

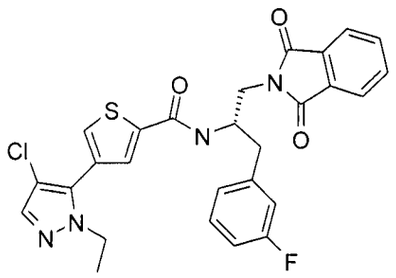
El compuesto del título se preparó en forma de un sólido de color amarillo de acuerdo con el procedimiento del Ejemplo 119, con la excepción de que se sustituyó 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (302 mg, 0,95 mmol) [preparada de acuerdo con el procedimiento de la Preparación 6]: LC-MS (ES) m/z 389 $(M+H)^+$, ^1H RMN (400 MHz, MeOD) δ ppm 2,04 - 2,15 (m, 3 H) 2,35 - 2,47 (m, 3 H) 2,99 - 3,02 (m, 2 H) 3,18 - 3,24 (m, 2 H) 3,86 - 3,96 (m, 3 H) 4,56 - 4,62 (m, 1H) 7,16 - 7,26 (m, 4 H) 8,07 (s, 1 H).

Ejemplo 230

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

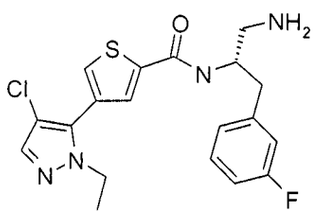


a) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



A una solución de ácido 4-(4-cloro-1-etil-1H-pirazol-5-il)-2-tiofenocarboxílico (220 mg, 0,857 mmol) [del Ejemplo 92] en DCM (5 ml) a 25ºC se le añadió en una porción PyBrOP (440 mg, 0,857 mmol), seguido de la adición de DIPEA (1,5 ml, 8,59 mmol). Después de 10 min, a la solución anterior se le añadió diamina 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (256 mg, 0,857 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (0,39 g, 81%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 537 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



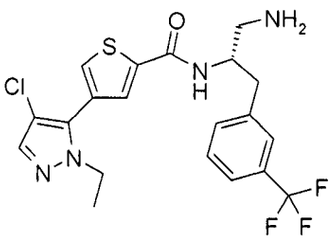
A TA, se añadió NH_2NH_2 (0,11 ml, 3,54 mmol) a 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (380 mg, 0,708 mmol) en MeOH (4 ml). Después de 10 h, el

disolvente se retiró al vacío para dar un residuo, que se disolvió en DCM (15 ml) y se lavó con H_2O (10 ml x 3).

A la solución en DCM anterior se le añadió HCl acuoso (12 N, 2,95 ml, 35,4 mmol). Después de 1 h, la fase acuosa se separó y se lavó con DCM (10 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (160 mg, 47%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H RMN (d_6-DMSO, 400 MHz) ppm 9,18-8,8(m, 1H), 8,28-8,08 (m, 4H), 8,04 (s, 1H), 7,27-7,43 (m, 1), 7,08-7,24 (m, 2H), 6,91-7,08 (m, 1H), 4,4-4,34 (m, 1H), 4,14 (c, J = 7,3 Hz, 2H), 3,15-2,80 (m, 4H) y 1,29 (t, J = 7,3 Hz, 3H).

Ejemplo 231

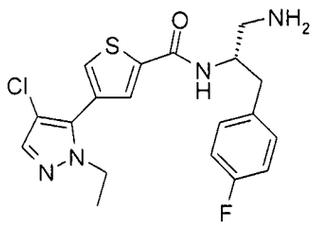
N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 230, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (339 mg, 0,97 mmol): LC-MS (ES) m/z = 457 $(M+H)^+$, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 7,92 (s a, 1H), 7,89-7,80 (m, 1H), 7,63-7,59 (m, 3H), 7,56-7,48 (m, 2H), 4,61-4,53 (m, 1H), 4,21-4,15 (m, 2H), 3,46-3,21 (m, 2H), 3,18-3,02 (m, 2H) y 1,35 (t, J = 7,3 Hz, 3H).

Ejemplo 232

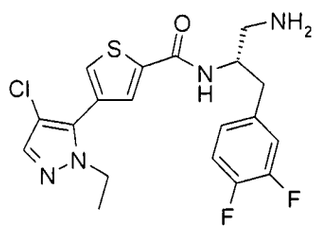
N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 230, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2*S*)-2-amino-3-(4-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (584 mg, 1,95 mmol): LC-MS (ES) m/z = 407 $(M+H)^+$, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 7,93 (d, J = 1,3 Hz, 1H), 7,85 (d, J = 1,3 Hz, 1H), 7,59 (s, 1H), 7,34-7,31 (m, 2H), 7,05-7,01 (m, 2H), 4,52 (m, 1H), 4,19 (c, J = 7,3 Hz, 2H), 3,26-3,12 (m, 2H), 3,05-2,94 (m, 2H) y 1,36 (t, J = 7,3 Hz, 3H).

Ejemplo 233

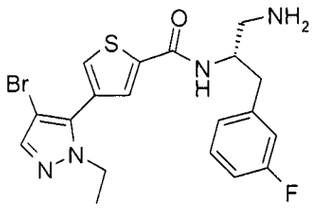
N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



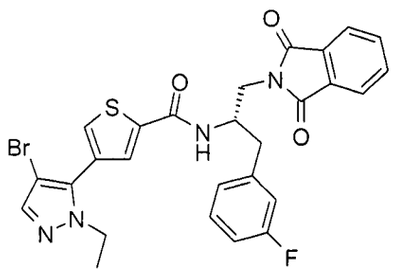
El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 230, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2*S*)-2-amino-3-(3,4-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (200 mg, 0,63 mmol): LC-MS (ES) m/z = 425 $(M+H)^+$, ^{1}H RMN (d_6-DMSO, 400 MHz) ppm 8,88 (d, J = 8,3 Hz, 1H), 8,16-8,06 (m, 4H), 7,71 (s, 1H), 7,39-7,30 (m, 2H), 7,12 (m, 1H), 4,35 (m, 1H), 4,14 (c, J = 7,1 Hz, 2H), 3,08-2,87 (m, 4H) y 1,29 (t, J = 7,1 Hz, 3H).

Ejemplo 234

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

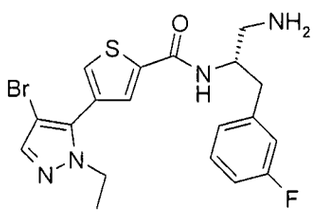


a) 4-(4-bromo-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 93, con la excepción de que se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (149 mg, 0,50 mmol): LC-MS (ES) m/z = 582 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

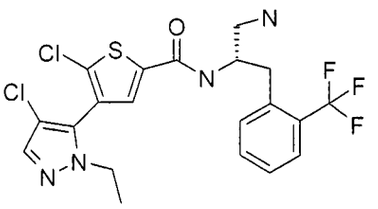


El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 230(b), con la excepción de que se sustituyó 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-

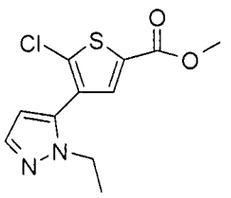
2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida por *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (240 mg, 0,41 mmol): LC-MS (ES) m/z = 452(M+H)$^+$, ^{1}H RMN (d_6-DMSO, 400 MHz) ppm 9,24-8,85 (m, 1H), 8,26-8,13 (m, 4H), 8,03 (s, 1H), 7,03 (s, 1H), 7,34 -7,29 (m, 1H), 7,16-7,13 (m, 2H), 7,05-7,00 (m, 1H), 4,39 (m, 1H), 4,14 (c, J = 7,3 Hz, 2H), 3,06-2,96 (m, 4H) y 1,28 (t, J = 7,3 Hz, 3H).

Ejemplo 235

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

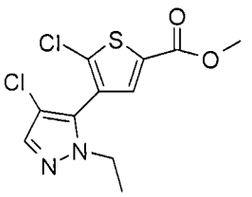


a) 5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



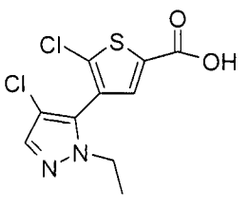
A una solución de 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (300 mg, 1,17 mmol) en THF (2 ml) se le añadieron Na_2CO_3 (2 M, 1,76 ml, 3,52 mmol), $Pd(dppf)Cl_2$ (86, 0,117 mmol) y 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (313 mg, 1,41 mmol). La mezcla de reacción se calentó a 80ºC en un tubo cerrado herméticamente en una atmósfera de N_2. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (EtOAc/Hex, 20-50%) para producir el compuesto del título (0,272 g, 82%) en forma de un jarabe de color amarillo claro: LC-MS (ES) m/z = 271 (M+H)$^+$.

b) 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



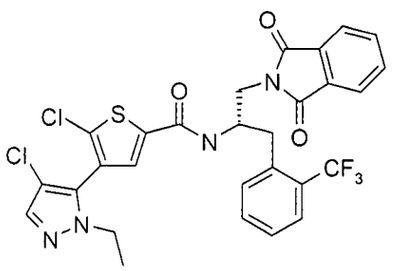
Se calentaron 5-cloro-4-[(1Z)-1-(1-etil-2-metilidenohidrazino)-1-propen-1-il]-2-tiofenocarboxilato de metilo (260 mg, 0,96 mmol) y 1-cloro-2,5-pirrolidinadiona (154 mg, 1,15 mmol) en THF (4 ml) a 70°C en una atmósfera de N_2 durante 2 h, se concentraron y se purificaron sobre sílice (EtOAc/Hex, 10-30%) para producir el compuesto del título (0,281 g, 83%) en forma de un jarabe: LC-MS (ES) m/z = 305 $(M+H)^+$.

c) ácido 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



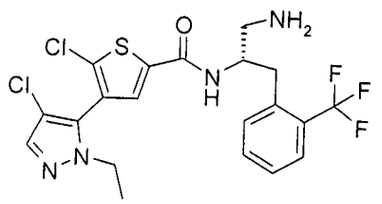
A una solución de 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (260 mg, 0,85 mmol) en THF/H_2O (4 ml/1 ml) se le añadió KOH (478 mg, 8,52 mmol). La mezcla de reacción se calentó a 58°C durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar un ácido bruto, que se usó directamente sin purificación adicional.

d) 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de ácido 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (~0,85 mmol) en DCM (5 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (477 mg, 1,02 mmol), seguido de la adición de DIPEA (0,744 ml, 4,26 mmol). Después de agitar durante 10 min, a la solución anterior se le añadió diamina 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (356 mg, 1,02 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (0,416 g, 79%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 621 $(M+H)^+$.

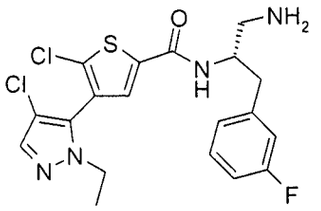
e) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1H-pirazol-5-il)-2-tiofenocarboxamida



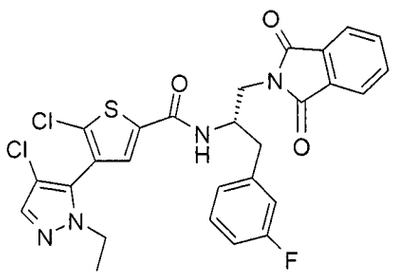
Se disolvió 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (410 mg, 0,66 mmol) en MeOH (2 ml) y la mezcla se trató con NH_2NH_2 (1,04 ml, 33 mmol). La reacción se agitó durante 5 h a TA, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se neutralizó con hidróxido de amonio. La mezcla se extrajo con DCM (5 ml x 3), se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título, que se disolvió en MeOH (2 ml), y se trató con HCl (4 M en dioxano, 1,6 ml). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (160 mg, 42%) en forma de una sal di-HCl: LC-MS: m/z = 491 $(M+H)^+$, ^{1}H RMN (d_6-DMSO, 400 MHz) ppm 9,34 (J = 8,8 Hz, 1H), 8,38-8,03 (m, 3H), 7,77 (s, 1H), 7,69-7,59 (m, 2H), 7,53 (dd, J = 7,3, 7,3 Hz, 1H), 7,42(dd, J = 7,6, 7,6 Hz, 1H), 4,48 (m, 1H), 4,13-4,00 (m, 2H), 3,17-2,90 (m, 4H) y 1,29 (m, 3H).

Ejemplo 236

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

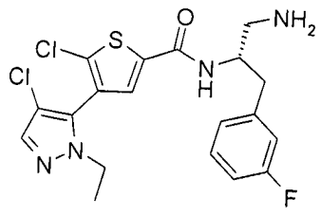


a) 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



A una solución de ácido 5-cloro-4-(4-cloro-1-etil-1H-pirazol-5-il)-2-tiofenocarboxílico (180 mg, 0,618 mmol) [del Ejemplo 235(c)] en DCM (5 ml) a 25°C se le añadió en una porción PyBrOP, seguido de la adición de DIPEA (0,54 ml, 3,09 mmol). Después de agitar durante 10 min, a la solución anterior se le añadió en una porción 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (203 mg, 0,68 mmol). Después de agitar durante 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (285 mg, 77%) en forma de un sólido de color blanco: LC-MS (ES) m/z = 571 $(M+H)^+$.

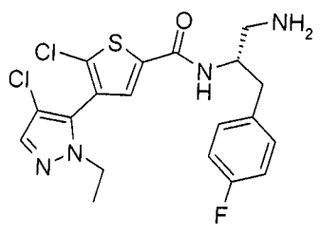
b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A TA, se añadió NH_2NH_2 (0,15 ml, 4,78 mmol) a 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (280 mg, 0,49 mmol) en MeOH (5 ml). Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se disolvió en DCM (15 ml), y se lavó con H_2O (10 ml x 3). A la solución en DCM se le añadió HCl (12 N, 1,0 ml). Después de 1 h, la fase acuosa se separó y se lavó con DCM (10 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (179 mg, 67,5%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z = 441 $(M+H)^+$, ^1H RMN (d_4-MeOD, 400 MHz) ppm 7,72-7,67 (m, 1H), 7,62 (s, 1H), 7,35-7,29 (m, 1H), 7,14-7,17 (m, 2H), 7,00-6,96 (m, 1H), 4,53 (m, 1H), 4,14-3,97 (m, 2H), 3,37-3,15 (m, 2H), 3,07-2,97 (m, 2H) y 1,33 (t, J = 7,1 Hz, 3H).

Ejemplo 237

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

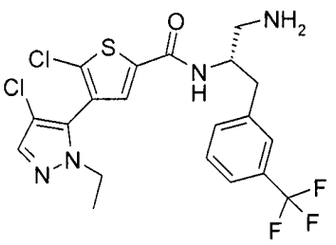


El compuesto del título (190 mg, 70%) se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 236, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2*S*)-2-amino-3-(4-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (231 mg, 0,77 mmol): LC-MS (ES) m/z 441 $(M+H)^+$, ^1H RMN (d_4-MeOD, 400 MHz, sin calibración del desplazamiento químico del pico de disolvente MeOD) ppm 6,09 (s, 1H), 6,08 (s, 1H), 5,78-5,75 (m, 2H), 5,53-5,48 (m, 2H), 2,96 (m, 1H), 2,51

(m, 2H), 1,71-1,67 (m, 1H), 1,62-1,54 (m, 1H), 1,49-1,38 (m, 2H) y -0,21 (t, J = 7,3 Hz, 3H).

Ejemplo 238

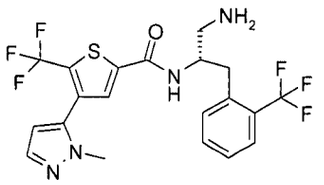
N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



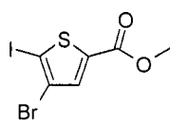
El compuesto del título (228 mg, 58,2%) se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 236, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (156 mg, 0,45 mmol): LC-MS (ES) m/z 491 $(M+H)^+$, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 7,66-7,49 (m, 6H), 4,60-4,47 (m, 1H), 4,09-4,01 (m, 2H), 3,36-3,18 (m, 2H), 3,16-3,01 (m, 2H) y 1,33 (t, J = 7,1 Hz, 3H).

Ejemplo 239

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxamida

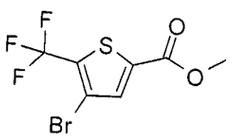


a) 4-bromo-5-yodo-2-tiofenocarboxilato de metilo



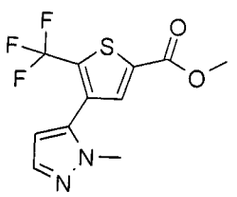
A -78°C, se añadió nBuLi (2,05 ml, 5,13 mmol) a una solución de 4,5-dibromo-2-tiofenocarboxilato de metilo (1,4 g, 4,67 mmol) en THF (10 ml). Después de que la mezcla se agitara durante 30 min, se añadió I_2 (1,185 g, 4,67 mmol) en 3 ml de THF. Después de agitar la solución resultante a -78°C durante 1 h, se inactivó con $Na_2S_2O_3$ a -78°C y se calentó a TA. La mezcla de reacción se extrajo con DCM, se secó sobre Na_2SO_4 y se concentró. El producto bruto se purificó sobre sílice (EtOAc/Hex, 0-10%) para dar el compuesto del título (1,3 g, 56%) en forma de un sólido de color amarillo: LC-MS (ES) m/z 348 $(M+H)^+$.

b) 4-bromo-5-(trifluorometil)-2-tiofenocarboxilato de metilo



A una solución de 4-bromo-5-yodo-2-tiofenocarboxilato de metilo (500 mg, 1,44 mmol), yoduro de cobre (I) (137 mg, 0,72 mmol) y fluoruro potásico (251 mg, 4,32 mmol) en DMF/HMPA (5 ml/5 ml) se le añadió difluoro(fluorosulfonil)acetato de metilo (1,1 g, 5,76 mmol). La mezcla se calentó a 70°C en una atmósfera de N_2 en un tubo cerrado herméticamente. Después de 1 h, la reacción se interrumpió con NH_4Cl (sat.) (2 ml), se extrajo con éter (5 ml x 5) y se lavó con agua destilada (5 ml x 5). La fase orgánica combinada se secó sobre Mg_2SO_4 y se purificó sobre sílice (EtOAc/Hex, 20-50%) para producir el compuesto del título (0,82 g) que contenía 60% de una impureza inseparable: LC-MS m/z (ES) 290 $(M+H)^+$.

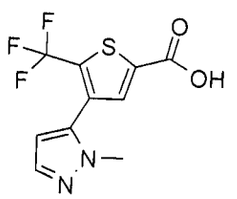
c) 4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxilato de metilo



Una mezcla de 4-bromo-5-(trifluorometil)-2-tiofenocarboxilato de metilo (0,8 g, pureza de 40%, 1,11 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (0,299 g, 1,434 mmol), tetraquis (0,128 g, 0,11 mmol) y K_2CO_3 (0,459 g, 3,32 mmol) en dioxano/H_2O (5 ml/1 ml) se calentó a 78°C en un tubo cerrado herméticamente. Después de 12 h, la mezcla de reacción se concentró al vacío y

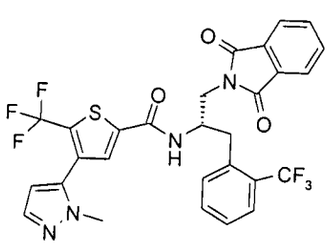
se purificó sobre sílice (EtOAc/Hex, 40-60%) para producir el compuesto del título (0,25 g, 70%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z 291 $(M+H)^+$.

d) ácido 4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxílico



A una solución de 4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxilato de metilo (250 mg, 0,77 mmol), en THF/H_2O (3 ml/0,3 ml) se le añadió KOH (217 mg, 3,88 mmol). La mezcla de reacción se calentó a 50°C durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido bruto (235 mg, puro al 80%) que se usó directamente en la siguiente etapa sin purificación adicional: LC-MS (ES) 277 $(M+H)^+$.

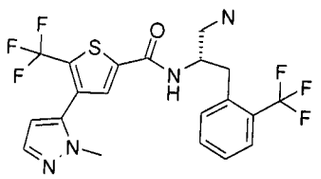
e) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxamida



A temperatura ambiente, una mezcla de ácido 4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxílico (235 mg, pureza de 80%, 0,68 mmol), hexafluorofosfato de fosfonio (PyBrOP) (381 mg, 0,19 mmol), DIPEA (0,59 ml, 3,4 mmol) y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (261 mg, 0,75 mmol) en DCM (5 ml) se agitó durante 2 h. La solución de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-

50%/Hexano), produciendo el compuesto del título (386 mg, 86%) en forma de un sólido de color blanco: LC-MS (ES) 607 $(M+H)^+$.

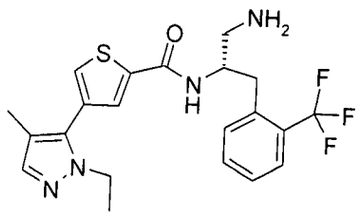
f) N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxamida



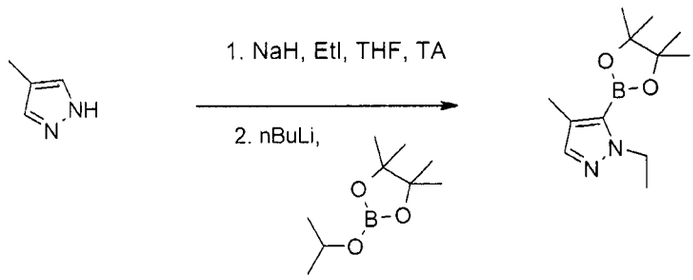
Se disolvió *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxamida (150 mg, 0,25 mmol) en MeOH (5 ml) y la mezcla se trató con NH_2NH_2 (0,76 ml, 24,2 mmol). La reacción se agitó durante 5 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se añadió hidróxido de amonio (0,32 ml, al 30% en peso, 2,46 mmol). La mezcla se extrajo con DCM (5 ml x 3), se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. El compuesto de la base libre se disolvió en MeOH (2 ml) y se trató con HCl (4 M en dioxano, 0,62 ml, 2,48 mmol). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (90 mg, 66%) en forma de un sólido de color blanco: LC-MS (ES) m/z 477 $(M+H)^+$, ^1H RMN (d_6-DMSO, 400 MHz) ppm 8,00 (d, J = 1,1 Hz, 1H), 7,77 (d, J = 1,8 Hz, 1H), 7,72 (d, J = 7,8 Hz, 1H), 7,59-7,52 (m, 2H), 7,44 (d, J = 7,4 Hz, 1H), 6,57 (d, J = 2,0 Hz, 1H), 4,67 (m, 1H), 3,87 (s, 3H) y 3,37-3,14 (m, 4H).

Ejemplo 240

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



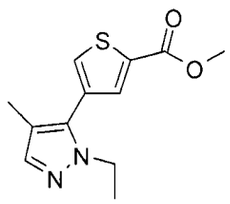
a) 1-etil-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol



A una suspensión de NaH (4,3 g, 60%, 108 mmol) en THF (200 ml) a TA se le añadió gota a gota 4-metil-1H-pirazol (6,8 g, 83 mmol). Después de 30 min, se añadió gota a gota EtI (8,03 ml, 99 mmol). Después de que se completara la reacción (2 h), la solución de reacción se diluyó con NH_4Cl acuoso saturado y se extrajo con éter. Las fracciones de éter se lavaron con agua (3 x 100 ml) y se secaron sobre $MgSO_4$.

A 0°C, a la solución en éter anterior de 4-metil pirazol se le añadió gota a gota n-BuLi (36,4 ml, 2,5 M en hexano, 91 mmol). La solución de reacción se agitó durante 1 hora a TA y después se enfrió a -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. A la solución de reacción se le añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (18,49 g, 99 mmol). Después de 15 min a -78°C, la reacción se dejó calentar a 0°C durante 1 hora. La reacción se diluyó con una solución saturada de NH_4Cl y se extrajo con DCM. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío para producir 1-etil-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (16 g, pureza de 80%) en forma de un jarabe que se usó sin purificación adicional: LC-MS (ES) m/z 155 $(M+H)^+$ para [RB(OH)2].

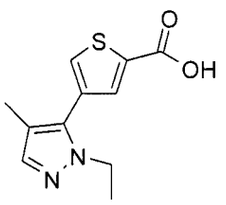
b) 4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una mezcla de 4-bromo-2-tiofenocarboxilato de metilo (300 mg, 1,36 mmol), 1-etil-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (449 mg, 1,9 mmol), $Pd(Ph_3P)_4$ (157 mg, 0,136 mmol) y K_2CO_3 (536 mg, 4,07 mmol) se calentó a

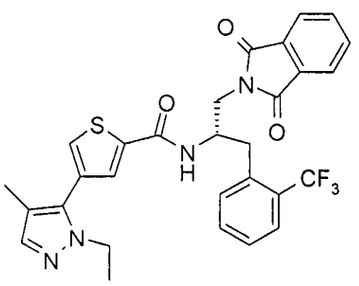
70°C durante 2 h, se concentró y se purificó sobre sílice (EtOAc/Hex, 10-30%) para producir el compuesto del título (0,27 g, 79%) en forma de un jarabe: LC-MS m/z = 251 $(M+H)^+$.

c) ácido 4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



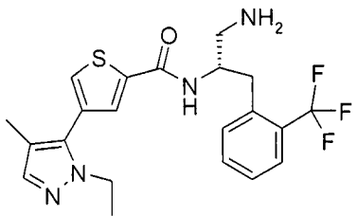
A una solución de 4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (270 mg, 1,08 mmol) en THF/H_2O (2 ml/0,4 ml) se le añadió KOH (303 mg, 1,79 mmol). La mezcla de reacción se calentó a 50°C durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido bruto (240 mg), que se usó directamente en la siguiente etapa sin purificación adicional: LC-MS m/z = 237 $(M+H)^+$.

d) N-((1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxamida.



A una mezcla de ácido 4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (240 mg, 1,02 mmol) y hexafluorofosfato de bromo-tris-pirrolidinofosfonio (Pybrop) (568 mg, 1,22 mmol) se le añadió DIPEA (1,77 ml, 10,16 mmol). Después de 10 min, se añadió 2-{(2S,4Z)-2-amino-4-[(1E)-1-(trifluorometil)-1-propen-1-il]-4,6-heptadien-1-il}-1H-isoindolo-1,3(2H)-diona (425 mg, 1,22 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (365 mg, 63%) en forma de un sólido de color blanco: LC-MS (ES) m/z 567 $(M+H)^+$.

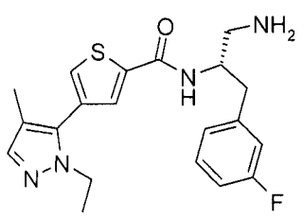
e) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



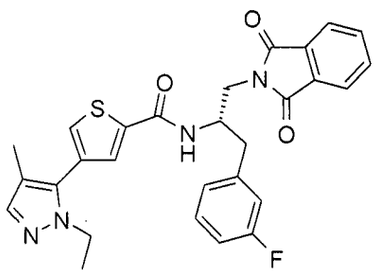
Se disolvió *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (365 mg, 0,64 mmol) en MeOH (8 ml) y la mezcla se trató con NH_2NH_2 (0,1 ml, 3,22 mmol). La reacción se agitó durante 5 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se añadió hidróxido de amonio (4,18 ml, 30% en peso, 32,2 mmol). La mezcla se extrajo con DCM (5 ml x 3), se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. El compuesto de la base libre se disolvió en MeOH (2 ml) y se trató con HCl (4 M en dioxano, 3,22 ml, 12,88 mmol). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (190 mg, 56,7%) en forma de un sólido de color blanco: LC-MS (ES) m/z 437 $(M+H)^+$, RMN (d_6-DMSO, 400 MHz) ppm 8,96 (m, 1H), 8,17-8,04 (m, 4H), 7,87 (s, 1H), 7,69 (d, J = 7,6 Hz, 1H), 7,62 (m, 1H), 7,53 (dd, J = 7,3, 7,3 Hz, 1H), 7,42 (d, J = 7,6 Hz, 1H), 7,38 (s, 1H), 4,50 (m, 1H), 4,09 (c, J = 7,3 Hz, 2H), 3,18-2,98 (m, 4H), 2,00 (s, 3H) y 1,27 (t, J = 7,3 Hz, 3H).

Ejemplo 241

(*N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

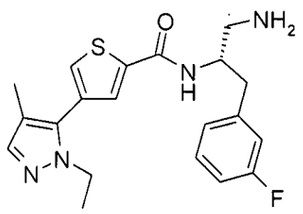


a) N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (125 mg, 0,53 mmol) [del Ejemplo 240(c)] en DCM (5 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (350 mg, 0,75 mmol), seguido de la adición de DIPEA (0,7 ml, 4,0 mmol). Después de 10 min, a la solución anterior se le añadió 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (180 mg, 0,60 mmol). Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (258 mg, 94%) en forma de un sólido de color blanco: LC-MS (ES) m/z 517 $(M+H)^+$.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



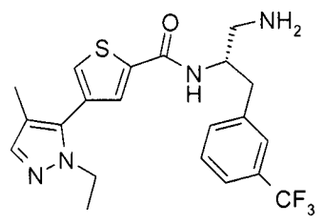
A TA, se añadió NH_2NH_2 (0,1 ml, 3,19 mmol) a N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (252 mg, 0,49 mmol) en MeOH (5 ml). Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se disolvió en DCM (10 ml) y se lavó con H_2O (10 ml x 3).

A la solución en DCM anterior se le añadió HCl (al 36%, 2 ml). Después de 1 h, la fase acuosa se separó y se lavó con DCM (10 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (170 mg, 72%) en forma de un sólido de

color blanquecino: LC-MS(ES) m/z 387 $(M+H)^+$, RMN (d_6-DMSO, 400 MHz) ppm 8,87 (d, J = 8,9 Hz, 1H), 8,08 (s a, 2H), 8,01 (s, 1H), 7,08 (s, 1H), 7,37 (s, 1H), 7,35-7,29 (m, 1H), 7,16-7,10 (m, 2H), 7,05-7,00 (m, 1H), 4,38 (m, 1H), 4,07 (c, J = 7,3 Hz, 2H), 3,04-2,94 (m, 4H), 2,00 (s, 3H) y 1,26 (t, J = 7,3 Hz, 3H).

Ejemplo 242

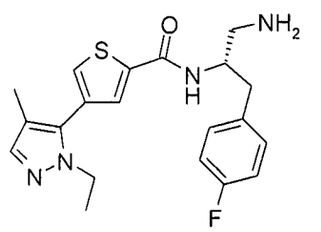
N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título (180 mg, 67%) se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 241, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (220 mg, 0,63 mmol): LC-MS (ES) m/z 437 $(M+H)^+$, RMN (d_6-DMSO, 400 MHz) ppm 8,96 (d, J = 8,84 Hz, 1H), 8,15 (m, 2H), 8,04 (d, J = 1,3 Hz, 1H), 7,86 (d, J = 1,3 Hz, 1H), 7,69-7,49 (m, 4H), 7,36 (s, 1H), 4,39 (m, 1H), 4,09 (c, J = 7,1 Hz, 2H), 3,11-3,00 (m, 4H), 1,99 (s, 3H) y 1,25 (t, J = 7,1 Hz, 3H).

Ejemplo 243

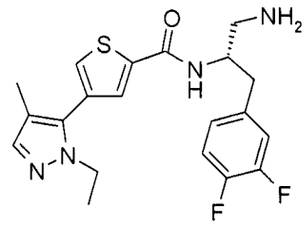
N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 241, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(4-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (160 mg, 0,536 mmol): LC-MS (ES) m/z 387 $(M+H)^+$, RMN (d_6-DMSO, 400 MHz) ppm 8,90 (d, J = 8,6 Hz, 1H), 8,13 (m, 2H), 8,03 (d, J = 1,3 Hz, 1H), 7,87 (d, J = 1,3 Hz, 1H), 7,38-7,30 (m, 3H), 7,12-7,08 (m, 2H), 4,36 (m, 1H), 4,07 (c, J = 7,1 Hz, 2H), 3,07-2,97 (m, 2H), 2,96-2,88 (m, 2H), 2,00 (s, 3H) y 1,25 (t, J = 7,1 Hz, 3H).

Ejemplo 244

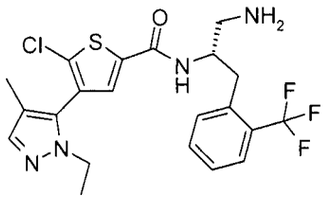
N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



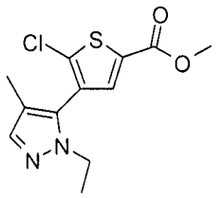
El compuesto del título (210 mg, 72%) se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 241, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(3,4-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (240 mg, 0,76 mmol): LC-MS (ES) m/z 405 $(M+H)^+$, RMN (d_6-DMSO, 400 MHz) ppm 8,99 (d, J = 8,34 Hz, 1H), 8,16 (m, 2H), 8,09 (d, J = 1,0 Hz, 1H), 7,87 (d, J = 1,0 Hz, 1H), 7,40-7,30 (m, 3H), 7,13 (s a, 1H), 4,36 (m, 1H), 4,08 (c, J = 7,3 Hz, 2H), 3,06-2,99 (m, 2H), 2,96-2,33 (m, 2H), 2,00 (s, 3H) y 1,26 (t, J = 7,3 Hz, 3H).

Ejemplo 245

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

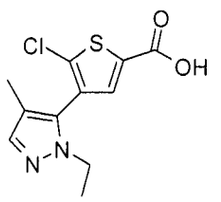


a) 5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



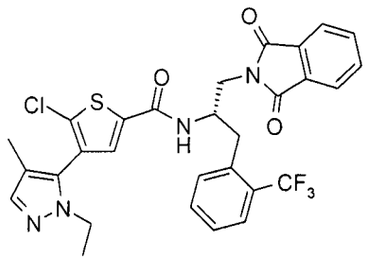
Una mezcla de 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (230 mg, 0,9 mmol), 1-etil-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (425 mg, 1,8 mmol), $PdCl_2$(dppf) (65,9 mg, 0,09 mmol) y carbonato sódico (ac. 2 N, 1,35 ml, 2,7 mmol) en THF (5 ml) se calentó a 70°C en un tubo cerrado herméticamente. Después de 5 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (EtOAc/Hex, 40-60%) para producir el compuesto del título (241 mg, 92%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z = 285 $(M+H)^+$.

b) ácido 5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



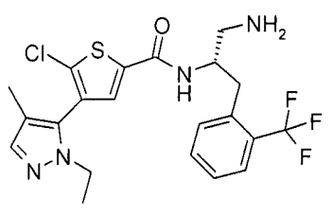
A una solución de 5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (260 mg, 0,90 mmol) en THF/H_2O (2 ml/2 ml) se le añadió KOH (201 mg, 3,6 mmol). La mezcla de reacción se calentó a 50°C durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido 5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico bruto, que se usó directamente sin purificación adicional: LC-MS (ES) m/z 271 $(M+H)^+$.

c) 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



Al ácido anterior en DCM (5 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (542 mg, 1,16 mmol), seguido de la adición de DIPEA (0,16 ml, 0,90 mmol). Después de 10 min, se añadió en una porción 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (312 mg, 0,90 mmol). Después de 2 h, la solución de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (278 mg, 49% en dos etapas) en forma de un sólido de color blanco: LC-MS (ES) m/z 601 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

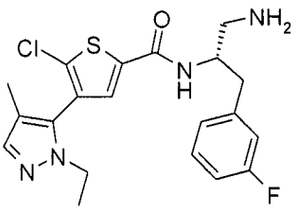


Se disolvió 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (255 mg, 0,42 mmol) en MeOH (2 ml) y la mezcla se trató con NH_2NH_2 (0,13 ml, 4,2 mmol). La reacción se agitó durante 5 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se añadió hidróxido de amonio. La mezcla se extrajo con DCM (5 ml x 3), se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. El compuesto de la base libre se disolvió en MeOH (1 ml) y se trató con HCl (4 M en dioxano, 2,1 ml).

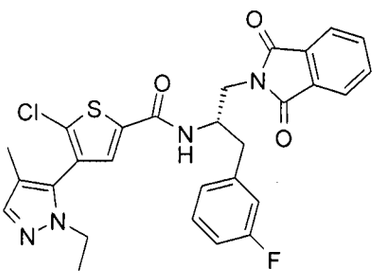
Después de agitar durante una noche, la mezcla se concentró para dar 120 mg del compuesto del título (120 mg, 49%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 471 (M+H)+, ^{1}H RMN (d_4-MeOD, 400 MHz) ppm 7,91 (s a, 2h), 7,71 (m, 1H), 7,59 (m, 1H), 7,53 (m, 1H), 7,44 (m, 1H), 4,65 (m, 1H), 4,21(m, 2H), 3,37-3,14 (m, 4H), 2,07 (s, 3H) y 1,40 (m, 3H).

Ejemplo 246

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

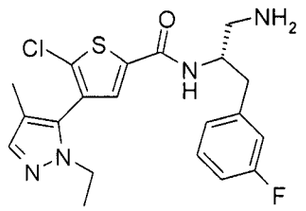


a) 5-cloro-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A una solución de ácido 5-cloro-4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxílico (130 mg, 0,48 mmol) [del Ejemplo 245(b)] en DCM (5 ml) a 25ºC se le añadió en una porción PyBrOP (250 mg, 0,54 mmol), seguido de la adición de DIPEA (0,7 ml, 4,01 mmol). Después de 10 min, a la solución anterior se le añadió 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (150 mg, 0,50 mmol). Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (210 mg, 79%) en forma de un sólido de color blanco: LC-MS m/z (ES) 551 $(M+H)^+$.

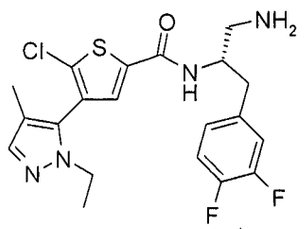
b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A TA, se añadió NH_2NH_2 (0,1 ml, 3,19 mmol) a 5-cloro-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (201 mg, 0,36 mmol) en MeOH (3 ml). Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se recogió en DCM (10 ml) y se lavó con H_2O (10 ml x 3). A la solución en DCM se le añadió HCl (al 36%, 2 ml). Después de 1 h, la fase acuosa se separó y se lavó con DCM (10 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (101 mg, 53%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 421 $(M+H)^+$, ^1H RMN (d_6-DMSO, 400 MHz) ppm 9,02 (d, J = 8,3 Hz, 1H), 8,08 (s, 2H), 7,97 (s, 1H), 7,42 (s, 1H), 7,32 (m, 1H), 7,15-7,09 (m, 1H), 7,06-7,01 (m, 1H), 4,35 (m, 1H), 3,95 (m, 2H), 3,05-2,98 (m, 2H), 2,96-2,88 (m, 2H) y 1,92 (s, 3H) y 1,24 (t, J = 6,6 Hz, 3H).

Ejemplo 247

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

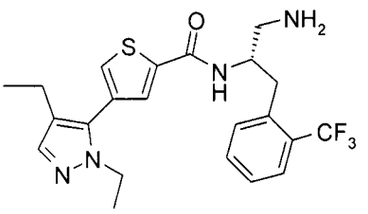


El compuesto del título (95 mg, 50,2%) se preparó de acuerdo con el procedimiento del Ejemplo 246, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(3,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (152 mg, 0,48 mmol): LC-MS (ES) m/z 439 $(M+H)^+$,^1H RMN (d_6-DMSO, 400 MHz) ppm 9,10 (d, J = 8,6 Hz, 1H), 8,13

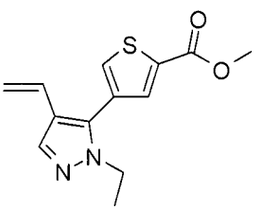
(s, 2H), 8,03 (s, 1H), 7,42 (s, 1H), 7,39-7,30 (m, 2H), 7,15-7,10 (m, 1H), 4,33 (m, 1H), 3,95 (m, 2H), 3,05-2,99 (m, 2H), 2,96-2,88 (m, 2H), 1,92, y 1,24 (t, J = 6,3 Hz, 3H).

Ejemplo 248

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dietil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

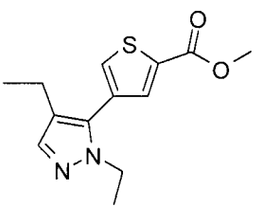


a) 4-(4-etenil-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



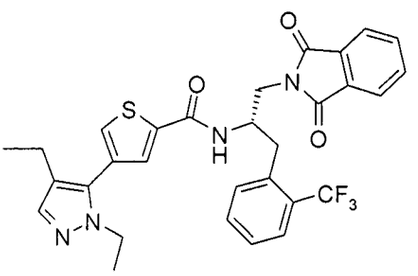
Una mezcla de 4-(4-bromo-1-etil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (200 mg, 0,64 mmol), $Pd(Ph_3P)_4$ (73,3 mg, 0,06 mmol) y tributil(etenil)estannano (302 mg, 0,95 mmol) se calentó a 90°C durante 1 h en una atmósfera de N_2 en un tubo cerrado herméticamente. La mezcla se purificó sobre sílice (EtOAc al 10%-20% en Hex) para dar el compuesto del título (151 mg, 76%): LC-MS (ES) m/z 263 $(M+H)^+$.

b) 4-(1,4-dietil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



Se añadió Pd/C (12 mg, al 10%) a una solución de 4-(4-etenil-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de etilo (150 mg, 0,57 mmol) en EtOH. El aire del sistema se retiró al vacío. La mezcla de reacción se agitó durante 10 h en una atmósfera de gas hidrógeno. La reacción se diluyó con MeOH (2 ml) y se filtró a través de Celite. La concentración de la solución de reacción dio el compuesto del título (149 mg, 94%) en forma de un aceite de color amarillo: LC-MS (ES) m/z 265 $(M+H)^+$.

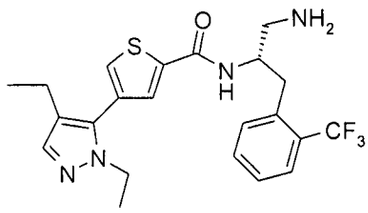
c) 4-(1,4-dietil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de 4-(1,4-dietil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (149 mg, 0,56 mmol) en THF/H_2O (5 ml/5 ml) se le añadió KOH (158 mg, 2,82 mmol). La mezcla de reacción se calentó a 50°C durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar un ácido bruto, que se usó directamente sin purificación adicional: LC-MS (ES) m/z 251 $(M+H)^+$.

Al ácido anterior en DCM (5 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (315 mg, 0,68 mmol), seguido de la adición de DIPEA (0,98 ml, 5,64 mmol) y 2-{(2S)-2-amino-3-[2-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (196 mg, 0,56 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (0,315 g, 94%) en forma de un sólido de color blanco: LC-MS (ES) m/z 581 $(M+H)^+$.

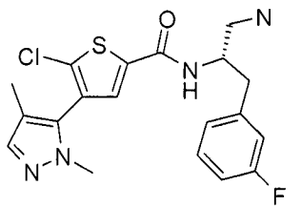
d) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dietil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



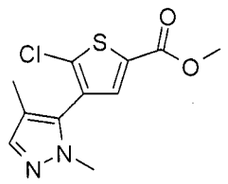
Se disolvió 4-(1,4-dietil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (310 mg, 0,53 mmol) en MeOH (1 ml) y la mezcla se trató con NH_2NH_2 (0,34 ml, 10,68 mmol). La reacción se agitó durante 5 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua (2 ml) y se añadió hidróxido de amonio (3,47 ml, 30%, 26,7 mmol). La mezcla se extrajo con DCM (5 ml x 3), se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. La base libre se disolvió en MeOH (1 ml) y se trató con HCl (4 M en dioxano, 2,1 ml). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (140 mg, 48%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 451 $(M+H)^+$, ^1H RMN (d_6-DMSO, 400 MHz) ppm 8,25-8,23 (m, 1H), 8,16-8,14 (m, 1H), 8,10-8,08 (m, 1H), 7,71-7,67 (m, 1H), 7,65-7,61 (m, 1H), 7,52-7,47 (m, 1H), 7,44-7,39 (m, 1H), 4,69 (m, 1H), 4,45-4,37 (m, 2H), 3,39-3,18 (m, 4H), 2,63-2,55 (m, 2H), 1,49-1,44 (m, 3H) y 1,24-1,19 (m, 3H).

Ejemplo 249

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



a) 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



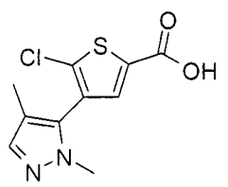
Método A:

A una solución de 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (500 mg, 1,96 mmol) en THF (10 ml) se le añadieron Na_2CO_3 acuoso (2 N, 3 ml, 6,0 mmol), $PdCl_2$(dppf) (143 mg, 0,196 mmol) y 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (522 mg, 2,35 mmol). La mezcla de reacción se calentó a 78ºC en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (EtOAc/Hex, 10-20%) para producir el compuesto del título (410 mg,77%) en forma de un sólido de color castaño: LC-MS (ES) m/z 271 $(M+H)^+$.

Método B:

A un matraz cerrado herméticamente de 250 ml se le añadieron 1,4-dimetil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (10,43 g, 47,0 mmol), carbonato potásico (16,23 g, 117 mmol), 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (10 g, 39,1 mmol) y bis(tri-t-butilfosfina)paladio (0) (1,6 g, 3,13 mmol) en 1,4-dioxano (120 ml) y H_2O (20 ml). Después de agitar durante 90 min a 70ºC, la solución de reacción se diluyó con DCM (100 ml) y se lavó con H_2O. La capa orgánica se secó Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice (hexanos/EtOAc, 10-30%) para dar el compuesto del título (7,6 g, 72%) en forma de un sólido de color castaño: LC-MS (ES) m/z 271 $(M+H)^+$.

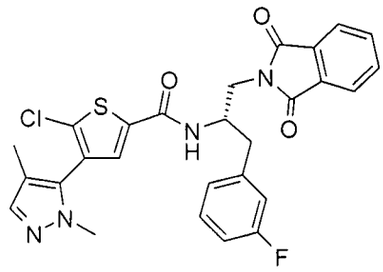
b) ácido 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxílico



A una solución de 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (7,6 g, 28,1 mmol) en THF/H_2O (30 ml/5 ml) se le añadió KOH (4,72 g, 84 mmol). La mezcla de reacción se calentó a 50ºC durante 1 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La

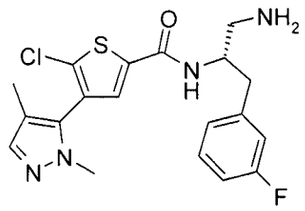
mezcla se extrajo con DCM (50 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido bruto (6,8 g, 94%), que se usó directamente en la siguiente etapa sin purificación adicional: LCMS (ES) m/z 257 $(M+H)^+$.

c) 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



A un matraz de fondo redondo de 500 ml se le añadieron ácido 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxílico (6,8 g, 26,5 mmol), 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (8,69 g, 29,1 mmol), N,N-diisopropil etilamina (14 ml, 80 mmol) y Pybrop (18,52 g, 39,7 mmol) en diclorometano (DCM) (100 ml). Después de agitar a TA durante 1 h, la solución de reacción se lavó con H_2O (2 x 100 ml) y la capa orgánica se secó Na_2SO_4, se filtró y se concentró. El producto bruto se añadió a una columna de gel de sílice y se eluyó con (EtOAc/hexanos, 1:1) para dar el compuesto del título (6,1 g, 42,9%) en forma de un sólido de color blanco: LCMS (ES) m/z 537 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



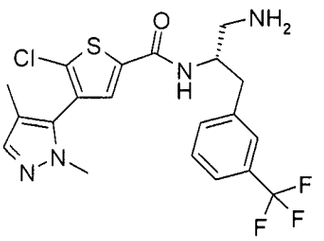
A TA, se añadió NH_2NH_2 (4 ml, 127 mmol) a 5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (5,2 g, 9,68 mmol) en MeOH (30 ml).

Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se recogió en DCM (200 ml) y se lavó con H_2O (50 ml x 5).

A la solución en DCM anterior se le añadió HCl (al 36%, 50 ml, 600 mmol). Después de 1 h, la fase acuosa se separó y se lavó con DCM (50 ml x 5). El agua se retiró a alto vacío para dar el compuesto del título (3,8 g, 79%) en forma de un sólido de color blanco: LC-MS (ES) m/z 407 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 8,75 (d, J = 8,8 Hz, 1H), 7,88 (s, 1H), 7,85 (m, 1H), 7,34-7,29 (m, 1H), 7,15-7,09 (m, 2H), 7,00-6,95 (m, 1H), 4,54 (m, 1H), 3,88 (s, 3H), 3,26-3,18 (m, 2H), 3,09-2,98 (m, 2H) y 2,08 (s, 3H).

Ejemplo 250

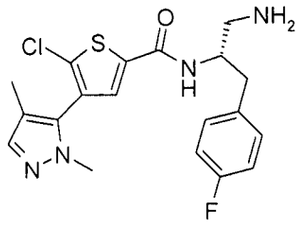
N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



El compuesto del título se preparó en forma de un sólido de color blanco (180 mg, 68%) de acuerdo con el procedimiento del Ejemplo 249, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-{(2S)-2-amino-3-[3-(trifluorometil)fenil]propil}-1H-isoindolo-1,3(2H)-diona (209 mg, 0,6 mmol): LC-MS (ES) m/z 457 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 7,94 (s, 1H), 7,90 (s, 1H), 7,65-7,60 (m, 2H), 7,55-7,48 (m, 2H), 4,55 (m, 1), 3,89 (s, 3H), 3,37-3,27 (m, 2H), 3,16-3,06 (m, 2H) y 2,08 (s, 3H).

Ejemplo 251

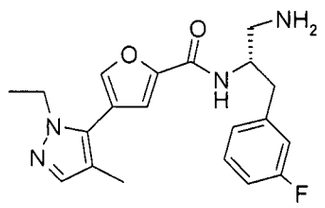
N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



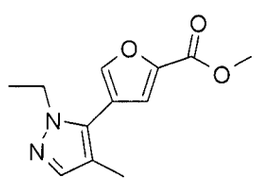
El compuesto del título se preparó en forma de un sólido de color blanco (95 mg, 39%) de acuerdo con el procedimiento del Ejemplo 249, con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-(4-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (584 mg, 1,96 mmol): LC-MS (ES) m/z 407 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 7,81 (s, 2H), 7,35-7,31 (m, 2H), 7,06-7,01 (m, 2H), 4,51 (m, 1H), 3,89 (s, 3H), 3,25-3,16 (m, 2H), 3,05-2,94 (m, 2H) y 2,07 (s, 3H).

Ejemplo 252

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-furanocarboxamida



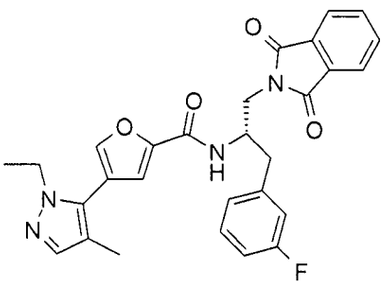
a) 4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



A una solución de 4-bromo-2-furanocarboxilato de metilo (500 mg, 2,439 mmol) en THF (5 ml) se le añadieron Na_2CO_3 acuoso (2 N, 3,6 ml, 7,2 mmol), $PdCl_2$(dppf) (160 mg, 0,22 mmol) y 1-etil-4-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (700 mg, 2,96 mmol). La mezcla de reacción se calentó a 78°C en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (EtOAc/Hex, 20-40%) para

producir el compuesto del título (460 mg, 76%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z 235 $(M+H)^+$.

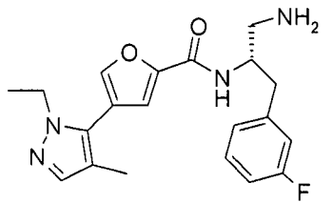
b) *N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-furanocarboxamida



A una solución de 4-(1-etil-4-metil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (210 mg, 0,90 mmol) en THF/H_2O (5 ml/0,5 ml) se le añadió KOH (200 mg, 3,56 mmol). La mezcla de reacción se calentó a 50°C durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O (2 ml), el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar un ácido bruto, que se usó directamente en la siguiente etapa sin purificación adicional: LC-MS (ES) m/z 221 $(M+H)^+$.

Al ácido 4-(1-etil-4-metil-1H-pirazol-5-il)-2-furanocarboxílico bruto en DCM (5 ml) a 25°C se le añadió en una porción PyBrOP (370 mg, 0,79 mmol), seguido de la adición de DIPEA (0,8 ml, 4,58 mmol). Después de 10 min, a la solución de reacción se le añadió 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (220 mg, 0,74 mmol). Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (164 mg, 54%) en forma de un sólido de color blanco: LC-MS (ES) m/z 501 $(M+H)^+$.

c) *N*-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1H-pirazol-5-il)-2-furanocarboxamida

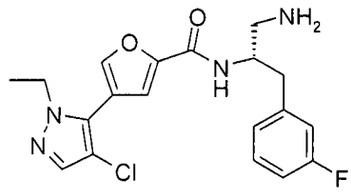


A TA, se añadió NH_2NH_2 (0,1 ml, 3,19 mmol) a una solución de N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1H-pirazol-5-il)-2-furanocarboxamida (150 mg, 0,3 mmol) en MeOH (5 ml). Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se recogió en DCM (10 ml) y se lavó con H_2O (10 ml x 3).

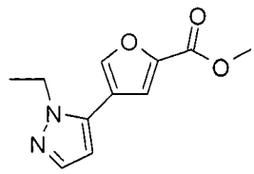
A la solución en DCM se le añadió HCl (al 36%, 1 ml, 12 mmol). Después de 1 h, la fase acuosa se separó y se lavó con DCM (10 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (80 mg, 57%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 371 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 8,19 (s, 1H), 8,05 (s, 1H), 7,44 (s, 1H), 7,32 (m, 1H), 7,16-7,08 (m, 2H), 6,97 (m, 1H), 4,62 (m, 1H), 4,37 (c, J = 7,1 Hz, 2H), 3,38-3,18 (m, 2H), 3,10-2,99 (m, 2H), 2,15 (s, 3H) y 1,46 (t, J = 7,1 Hz, 3H).

Ejemplo 253

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida



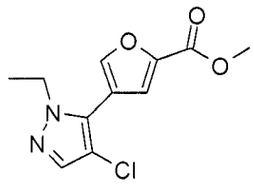
a) 4-(1-etil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



A una solución de 4-bromo-2-furanocarboxilato de metilo (1,0 g, 4,88 mmol) en THF (20 ml) se le añadieron Na_2CO_3 acuoso (2 N, 8 ml, 16 mmol), $PdCl_2$(dppf) (0,35 g, 0,49 mmol) y 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol

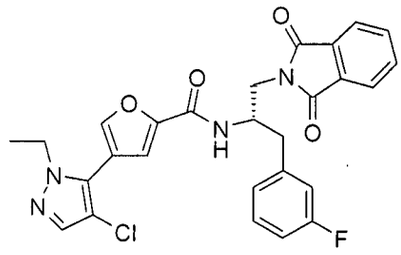
(1,3 g, 5,85 mmol). La mezcla de reacción se calentó a 78ºC en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró al vacío y se purificó sobre sílice (EtOAc/Hex, 20-40%) para producir el compuesto del título (0,8 g, 74,5%) en forma de un sólido de color amarillo claro: LC-MS (ES) m/z = 221 $(M+H)^+$.

b) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



Una mezcla de 4-(1-etil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (300 mg, 1,36 mmol) y NCS (218 mg, 1,63 mmol) en THF (5 ml) se calentó a 70ºC en un tubo cerrado herméticamente. Después de 5 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 10-20%/Hexano), produciendo el compuesto del título (260 mg, 75%) en forma de un sólido de color blanco: LC-MS (ES) m/z 255 $(M+H)^+$.

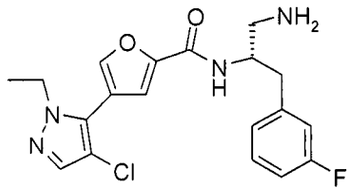
c) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-furanocarboxamida



A una solución de 4-(4-cloro-1-etil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (250 mg, 0,98 mmol) en THF/H_2O (5 ml/0,5 ml) se le añadió KOH (200 mg, 3,56 mmol). La mezcla de reacción se calentó a 58ºC durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O (2 ml), el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar un ácido bruto, que se usó directamente sin purificación adicional: LC-MS (ES) m/z 241 $(M+H)^+$.

Al ácido bruto anterior en DCM (5 ml) a 25ºC se le añadió en una porción PyBrOP (550 mg, 1,18 mmol), seguido de la adición de DIPEA (0,7 ml, 4,01 mmol). Después de 10 min, a la solución de reacción se le añadió 2-[(2S)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (322 mg, 1,08 mmol). Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 20-50%/Hexano), produciendo el compuesto del título (360 mg, 70%) en forma de un sólido de color blanco: LC-MS (ES) m/z 521 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida

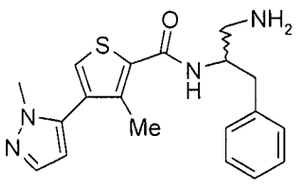


A TA, se añadió NH_2NH_2 (0,15 ml, 4,78 mmol) a una solución de 4-(4-cloro-1-etil-1H-pirazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-furanocarboxamida (350 mg, 0,67 mmol) en MeOH (5 ml). Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se recogió en DCM (15 ml) y se lavó con H_2O (10 ml x 3).

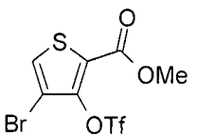
A la solución en DCM anterior se le añadió HCl (al 36%, 2 ml, 23,7 mmol)). Después de 1 h, la fase acuosa se separó y se lavó con DCM (10 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (260 mg, 78%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 391 $(M+H)^+$. RMN (d_6-DMSO, 400 MHz) ppm 8,70 (m, 1H), 8,29 (s, 1H), 8,02 (m, 2H), 7,70 (s, 1H), 7,50-7,45 (m, 1H), 7,36-7,30 (m, 1H), 7,14-7,08 (m, 2H), 7,06-7,01 (m, 1H), 4,43 (m, 1H), 4,16 (c, J = 7,3 Hz, 2H), 3,04-2,88 (m, 4H) y 1,30 (t, J = 7,3 Hz, 3H).

Ejemplo 254

N-[2-amino-1-(fenilmetil)etil]-3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

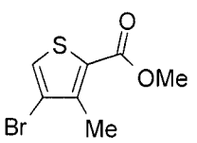


a) 4-bromo-3-{[(trifluorometil)sulfonil]oxi}-2-tiofenocarboxilato de metilo



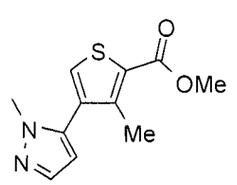
A una solución de 4-bromo-3-{[(trifluorometil)sulfonil]oxi}-2-tiofenocarboxilato de metilo (0,948 g, 4,0 mmol) en CH_2Cl_2 (5 ml) y piridina (1 ml) a 0°C se le añadió Tf_2O (1,0 ml, 6,0 mmol). La mezcla se agitó durante 1 h, se vertió sobre agua enfriada con hielo (10 ml) y se extrajo con CH_2Cl_2 (5 ml x 3). Las capas orgánicas recogidas se secaron (Na_2SO_4) y se concentraron para dar un jarabe de color rojo que se usó directamente en la siguiente etapa sin purificación adicional: LC-MS (ES) m/z 370 $(M+H)^+$.

b) 4-bromo-3-metil-2-tiofenocarboxilato de metilo



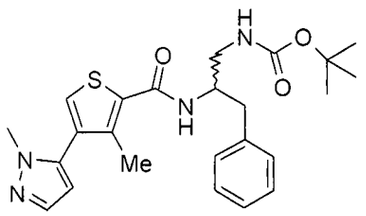
A una solución de 4-bromo-3-{[(trifluorometil)sulfonil]oxi}-2-tiofenocarboxilato de metilo (825 mg, 2,25 mmol) en dioxano/H_2O (5 ml/1 ml) se le añadieron K_2CO_3 (930 mg, 6,75 mmol), tetraquistrifenilfosfina Pd(0) (260 mg, 0,22 mmol) y ácido metilborónico (175 mg, 2,91 mmol). La mezcla de reacción se calentó a 78°C en un tubo cerrado herméticamente durante 12 h. La solución de reacción se concentró al vacío y se purificó sobre gel de sílice (hexanos/EtOAc, 9:1) para dar el compuesto del título (441 mg, 84%) en forma de un sólido pardo: LC-MS (ES) m/z 236 $(M+H)^+$.

c) 4-[1-(dimetilamino)etenil]-3-metil-2-tiofenocarboxilato de metilo



A una solución de 4-bromo-3-metil-2-tiofenocarboxilato de metilo (300 mg, 1,27 mmol) en dioxano/H_2O (5 ml/1 ml) se le añadieron K_2CO_3 (525 mg, 3,80 mmol), tetraquistrifenilfosfina Pd(0) (15 mg, 0,01 mmol) y 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (345 mg,1,7 mmol). La mezcla de reacción se calentó a 70°C en un tubo cerrado herméticamente durante 2 h. La solución de reacción se concentró al vacío y se purificó sobre gel de sílice (hexanos/EtOAc, de 9:1 a 4:1) para dar el compuesto del título (270 mg, 90%): LC-MS (ES) m/z 237 $(M+H)^+$.

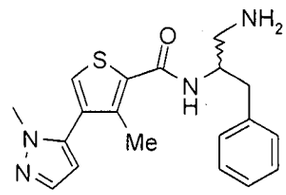
d) [2-({[3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



A una solución de 4-[1-(dimetilamino)etenil]-3-metil-2-tiofenocarboxilato de metilo (50 mg, 0,21 mmol) en THF/H_2O (2 ml/0,5 ml) se le añadió KOH (122 mg, 2,1 mmol). La mezcla resultante se calentó a 50°C durante 2 h. El THF se retiró al vacío y la capa acuosa se acidificó con HCl 6 N a un valor de pH de 3 y se extrajo con CH_2Cl_2 (5 ml x 3). Las fracciones orgánicas se secaron sobre Na_2SO_4 y se concentraron para dar el ácido 3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico bruto, que se usó directamente en la siguiente etapa.

A una solución del ácido 3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxílico bruto en DCM (2 ml) se le añadieron PyBrop (0,14 g, 0,3 mmol) y DIPEA (0,1 ml, 0,57 mmol). Después de 15 min, a la reacción se le añadió en una porción (2-amino-3-fenilpropil)carbamato de 1,1-dimetiletilo y se agitó durante 2 h a TA. La solución de reacción se concentró al vacío y se purificó sobre gel de sílice (EtOAc /Hexano, 20-50%) para dar el compuesto del título (51 mg, 49% en dos etapas) en forma de un sólido: LC-MS (ES) m/z 455 $(M+H)^+$.

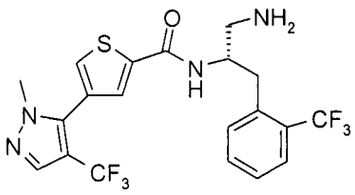
e) *N*-[2-amino-1-(fenilmetil)etil]-3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



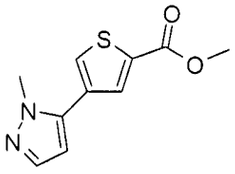
A una solución de [2-({[3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (51 mg, 0,11 mmol) en DCM (1 ml) se le añadió TFA (1 ml). La reacción se agitó durante 5 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40-10%) para producir la sal bis-TFA del compuesto del título. (16 mg, 41%): LC-MS (ES) m/z 355 $(M+H)^+$. RMN (d_4-MeOD, 400 MHz) ppm 7,64 (s, 1H), 7,56 (d, J = 1,8 Hz, 1H), 7,36-7,30 (m, 4H), 7,28-7,21 (m, 1H), 6,30 (d, J = 2,0 Hz, 1H), 4,58 (m, 1H), 3,69 (s, 3H), 3,27-3,13 (m, 2H), 3,07-2,93 (m, 2H) y 2,13 (s, 3H).

Ejemplo 255

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxamida



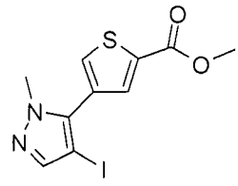
a) 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 4-bromo-2-tiofenocarboxilato de metilo (1,0 g, 4,5 mmol) en dioxano/H_2O (5:1, 12 ml) se le añadieron K_2CO_3 (1,86 mg, 13,5 mmol), tetraquistrifenilfosfina Pd(0) (300 mg, 0,25 mmol) y 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (1,23 g, 5,9 mmol). La mezcla de reacción se calentó a 75ºC en un tubo cerrado herméticamente durante 2 h. La mezcla de reacción se concentró y se purificó sobre gel de sílice (EtOAc/Hex 10-40%) para

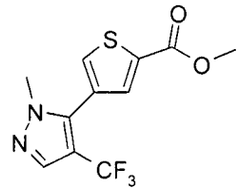
dar el compuesto del título (701 mg, 70%) en forma de un sólido de color blanco: LC-MS (ES) m/z 223 $(M+H)^+$.

b) 4-(4-yodo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



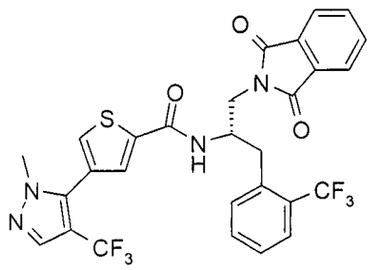
A una solución de 4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (700 mg, 3,15 mmol) en THF (5 ml) se le añadió en una porción NIS (922 mg, 4,09 mmol). La mezcla de reacción se agitó a 75°C durante 10 h y después se enfrió a temperatura ambiente. La mezcla de reacción se concentró y se purificó sobre gel de sílice (EtOAc/Hex 10-20%) para dar el compuesto del título (470 mg, 43%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 350 $(M+H)^+$.

c) 4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxilato de metilo



A una solución de 4-(4-yodo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (470 mg, 1,35 mmol), yoduro de cobre (I) (256 mg, 1,35 mmol) y fluoruro potásico (78 mg, 1,35 mmol) en DMF anhidra/HMPA (2 ml/2 ml) se le añadió trietil(trifluorometil)silano (745 mg, 4,04 mmol). La mezcla se calentó a 70°C en una atmósfera de N_2 en un tubo cerrado herméticamente. Después de 10 h, la reacción se interrumpió con NH_4Cl (sat.) (2 ml), se extrajo con éter (5 ml x 5) y se lavó con agua destilada (5 ml x 5). La fase orgánica combinada se secó sobre Mg_2SO_4 y se purificó sobre sílice (EtOAc/Hex, 10-30%) para producir el compuesto del título (0,29 g, 74%) en forma de un jarabe de color amarillo: LC-MS (ES) m/z 291 $(M+H)^+$.

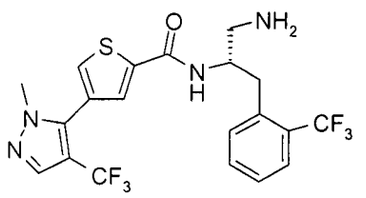
d) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxamida



A una solución de 4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxilato de metilo (150 mg, 0,52 mmol) en THF/H_2O (2 ml/0,5 ml) se le añadió KOH (116 mg, 2,0 mmol). La mezcla de reacción se calentó a 50°C durante 2 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido bruto, que se usó directamente en la siguiente etapa sin purificación adicional: LC-MS (ES) m/z 277 $(M+H)^+$.

Al ácido anterior en DCM (5 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (279 mg, 0,59 mmol), seguido de la adición de DIPEA (0,5 ml, 2,87 mmol) y 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (174 mg, 0,5 mmol). Después de 2 h, la solución se concentró y se purificó por cromatografía en columna (sílice, MeOH al 1-10%/$CHCl_3$), produciendo el compuesto del título (0,21 g, 67% en 2 etapas): LC-MS (ES) m/z 607 $(M+H)^+$.

e) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxamida

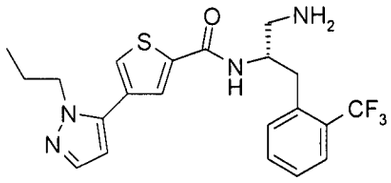


Se disolvió *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxamida (210 mg, 0,35 mmol) en MeOH (2 ml) y la mezcla se trató con NH_2NH_2 (0,5 ml, 15,9 mmol). La reacción se agitó durante 10 h, se concentró y se

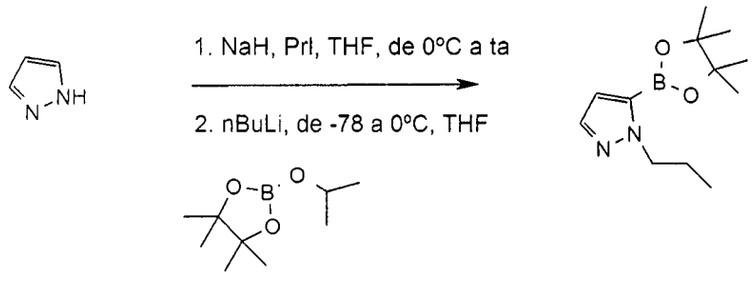
purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 40-10%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se neutralizó con hidróxido de amonio. La mezcla se extrajo con DCM, se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. El compuesto de la base libre se disolvió en MeOH y se trató con HCl (ac.). Después de agitar durante una noche, la reacción se concentró para dar el compuesto del título (95 mg, 57%) en forma de un sólido de color blanco. LC-MS: LC-MS (ES) m/z 477 $(M+H)^+$. RMN (d_6-DMSO, 400 MHz): δ ppm 8,92 (d, J = 9,1 Hz, 1H), 8,06 (m, 4H), 7,99 (s, 1H), 7,69 (d, J = 7,6 Hz, 1H), 7,59 (d, J = 7,6 Hz, 1H), 7,53 (m, 1H), 7,43 (m, 1H), 4,49 (m, 1H), 3,83 (s, 3H) y 3,14-2,99 (m, 4H).

Ejemplo 256

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



a) 1-propil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol

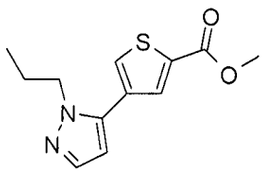


A una suspensión de NaH (al 60% en aceite mineral, 4,0 g, 100 mmol) en THF (200 ml) se le añadió en porciones 1H-pirazol (6,8 g, 100 mmol) a 0°C. Después de agitar a TA durante 1 h, se añadió gota a gota PrI (17,85 g, 105 mmol) a 0°C. La mezcla de reacción se agitó durante 10 h y se controló por LC-MS: m/e = 111 $(M+H)^+$. Después de que se completara la reacción, el NaI se retiró por

filtración. La solución en THF resultante que contenía 1-propil-1*H*-pirazol se usó directamente en la siguiente etapa.

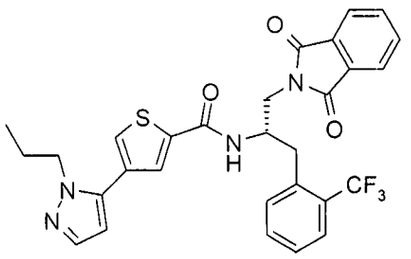
A la solución en THF anterior de 1-propil-1*H*-pirazol se le añadió n-BuLi (2,5M en hexano, 40 ml, 100 mmol) a -78°C. La solución de reacción se agitó durante 2 horas a TA y después se enfrió de nuevo a -78°C [*J. Heterocyclic Chem.* **41**, 931 (2004)]. A la solución de reacción se le añadió 2-isopropoxi-4,4,5,5-tetrametil-1,3,2-dioxaborolano (18,6 g, 100 mmol). Después de 30 min a -78°C, la reacción se interrumpió con una solución saturada de NH_4Cl y se extrajo con DCM. Los extractos orgánicos se secaron sobre Na_2SO_4 y se concentraron al vacío para producir el compuesto del título en forma de un sólido pardo que se usó directamente sin purificación adicional: LC-MS (ES) m/z 154 $(M+H)^+$ para [RB(OH)2].

b) 4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



A una solución de 4-bromo-2-tiofenocarboxilato de metilo (221 mg, 1,0 mmol) en dioxano/H_2O (5:1, 6 ml) se le añadieron K_2CO_3 (414 mg, 3,0 mmol), tetraquistrifenilfosfina Pd(0) (60 mg, 0,05 mmol) y 1-propil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-pirazol (404 mg, 1,5 mmol). La mezcla de reacción se calentó a 78°C en un tubo cerrado herméticamente durante 2 h. La mezcla de reacción se concentró y se purificó sobre gel de sílice (EtOAc/Hex, 10-40%) para dar el compuesto del título (176 mg, 70%) en forma de un sólido de color blanco: LC-MS (ES) m/z 251 $(M+H)^+$.

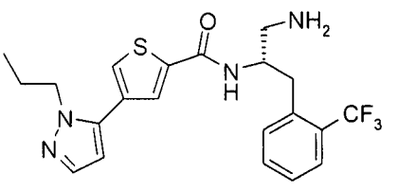
c) *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



A una solución de 4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (160 mg, 0,64 mmol) en THF/H_2O (2 ml/1 ml) se le añadió KOH (151 mg, 2,56 mmol). La mezcla de reacción se calentó a 50ºC durante 2 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido bruto, que se usó directamente en la siguiente etapa sin purificación adicional. LCMS (ES) m/z = 237 $(M+H)^+$.

Al ácido anterior en DCM (2 ml) a 25ºC se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (298 mg, 0,64 mmol), seguido de la adición de DIPEA (0,2 ml, 1,15 mmol) y 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (208 mg, 0,6 mmol). Después de 1 h, la solución se concentró y se purificó por cromatografía en columna (sílice, MeOH al 1-10%/$CHCl_3$), produciendo el compuesto del título (0,22 g, 61% en 2 etapas): LC-MS (ES) m/z 567 $(M+H)^+$.

d) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

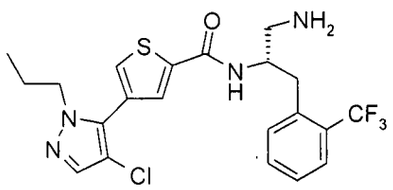


Se disolvió *N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (220 mg, 0,36 mmol) en MeOH (2 ml) y la mezcla se trató con NH_2NH_2 (0,3 ml, 9,56 mmol). La reacción se agitó durante 10 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se neutralizó con

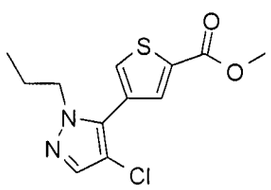
hidróxido de amonio. La mezcla se extrajo con DCM, se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. El compuesto de la base libre se disolvió en MeOH (2 ml) y se trató con HCl (4 M en dioxano). Después de agitar durante una noche, la solución de reacción se concentró para dar el compuesto del título (112 mg, 57%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 437 $(M+H)^+$, RMN (d_6-DMSO, 400 MHz): δ ppm 9,06-8,99 (m, 1H), 8,23-8,02 (m, 4H), 7,92 (s a, 1H), 7,69 (d, J = 7,8 Hz, 1H), 7,62-7,49 (m, 3H), 7,42 (m, 1H), 4,50 (m, 1H), 4,20 (m, 2H), 3,15-2,99 (m, 4H), 1,74 (m, 2H) y 0,80 (t, J = 7,3 Hz, 3H).

Ejemplo 257

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

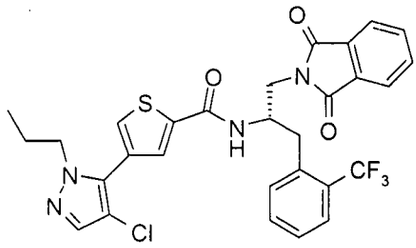


a) 4-(4-cloro-1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



Una mezcla de 4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (250 mg, 1,0 mmol) y NCS (200 mg, 1,5 mmol) en THF (5 ml) se calentó a 70°C en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 10%/Hexano), produciendo el compuesto del título (199 mg, 70%) en forma de un sólido de color blanco: LC-MS (ES) m/z 285 $(M+H)^+$.

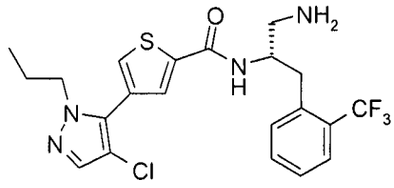
b) 4-(4-cloro-1-propil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida



A una solución de 4-(4-cloro-1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo (199 mg, 0,7 mmol) en THF/H_2O (2 ml/0,5 ml) se le añadió KOH (100 mg, 1,7 mmol). La mezcla de reacción se calentó a 50°C durante 2 h. Después de que la mezcla se concentrara y se diluyera con H_2O, el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (5 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar el ácido bruto, que se usó directamente en la siguiente etapa sin purificación adicional: LC-MS (ES) m/z 271 $(M+H)^+$.

Al ácido anterior en DCM (5 ml) a 25°C se le añadió en una porción hexafluorofosfato de bromo-tris-pirrolidinofosfonio (PyBrOP) (326 mg, 0,7 mmol), seguido de la adición de DIPEA (0,3 ml, 1,15 mmol) y 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (232 mg, 0,7 mmol). Después de 10 min, la solución se concentró y se purificó por cromatografía en columna (sílice, MeOH al 1-10%/$CHCl_3$), produciendo el compuesto del título (312 mg, 74% en 2 etapas): LC-MS (ES) m/z 601 $(M+H)^+$.

c) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

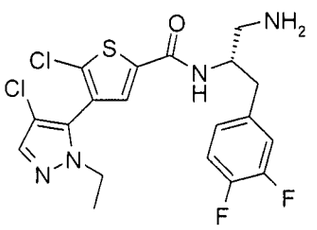


Se disolvió 4-(4-cloro-1-propil-1*H*-pirazol-5-il)-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-2-tiofenocarboxamida (312 mg, 0,52 mmol) en MeOH (2 ml) y la mezcla se trató con NH_2NH_2 (0,5 ml, 15,9 mmol). La reacción se agitó durante 10 h, se concentró y se purificó por HPLC de fase inversa (columna C18: H_2O/CH_3CN, 95-5%) para producir la sal bis-TFA del compuesto del título. La sal bis-TFA se disolvió en agua y se neutralizó con

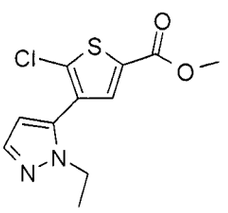
hidróxido de amonio. La mezcla se extrajo con DCM, se secó sobre Na_2SO_4 y se concentró para dar una base libre del compuesto del título. El compuesto de la base libre se disolvió en MeOH (2 ml) y se trató con HCl (ac.). Después de agitar durante una noche, la reacción se concentró para dar el compuesto del título (185 mg, 66%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 471 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 7,92 (m, 2H), 7,74-7,68 (m, 1H), 7,60 (s, 1H), 7,58-7,51 (m, 2H), 7,45-7,41 (m, 1H), 4,67 (m, 1H), 4,15 (t, J = 7,1 Hz, 2H), 3,37-3,09 (m, 4H), 1,77 (m, 2H) y 0,82 (t, J = 7,6 Hz, 3H).

Ejemplo 258

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



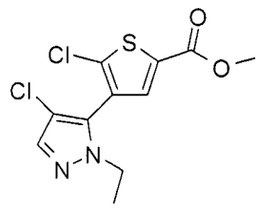
a) 5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



A un matraz cerrado herméticamente de 100 ml se le añadieron 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,61 g, 11,74 mmol), carbonato potásico (3,25 g, 23,48 mmol), 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (2 g, 7,83 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,4 g, 0,78 mmol) en 1,2-dimetoxietano (DME) (50 ml) y H_2O (10 ml). Después de agitar durante 3 h a 70ºC, la solución de reacción se diluyó con DCM (100 ml) y se lavó con H_2O. La capa orgánica se secó Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel

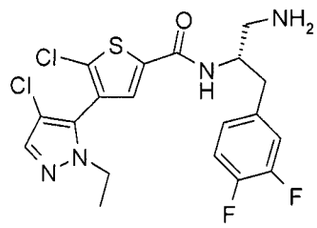
de sílice [EtOAc/hexanos, 10-30%] para dar el producto [1,8 g, 85%] en forma de un sólido de color blanquecino: LC-MS (ES) m/z 271 $(M+H)^+$.

b) 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxilato de metilo



Se calentaron 5-cloro-4-(1-etil-1H-pirazol-5-il)-2-tiofenocarboxilato de metilo (1,8 g, 6,65 mmol) y NCS (1,3 g, 9,74 mmol) en THF (10 ml) a 70°C en una atmósfera de N_2 durante 2 h. La solución de reacción se concentró y se purificó sobre sílice (EtOAc/Hex, 10-30%) para producir el compuesto del título (1,5 g, 74%) en forma de un jarabe: LC-MS (ES) m/z 305 $(M+H)^+$.

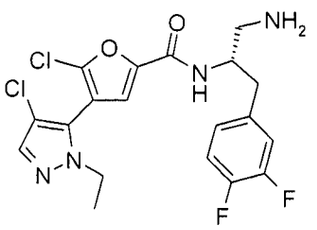
b) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida



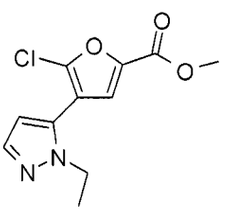
El compuesto del título (290 mg, 58,4%) se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 236, con la excepción de que se sustituyó 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida por 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-2-tiofenocarboxamida (526 mg, 1,662 mmol): LC-MS (ES) m/z 459 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 7,76 (m, 1H), 7,62 (s, 1H), 7,28-7,22 (m, 1H), 7,20-7,10 (m, 2H), 4,52 (m, 1H), 4,07 (m, 2H), 3,27-3,16 (m, 2H), 3,05-2,94 (m, 2H) y 1,34 (m, 3H).

Ejemplo 259

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida

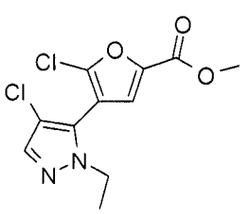


a) 5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



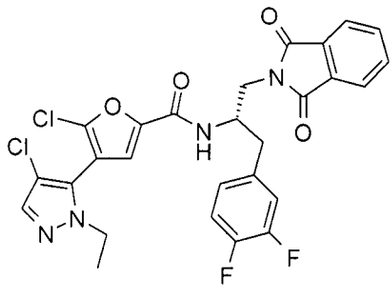
A un matraz cerrado herméticamente de 100 ml se le añadieron 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,61 g, 11,74 mmol), carbonato potásico (3,25 g, 23,48 mmol), 4-bromo-5-cloro-2-furanocarboxilato de metilo (1,85 g, 8,33 mmol) y bis(tri-t-butilfosfina)paladio (0) (0,16 g, 0,31 mmol) en 1,2-dimetoxietano (DME) (30 ml) y H_2O (5 ml). Después de agitar durante 2 h a 75°C, la solución de reacción se diluyó con DCM (100 ml) y se lavó con H_2O. La capa orgánica se secó Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice [EtOAc/hexanos, 10-30%] para dar el producto (0,8 g, 50,1%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 255 $(M+H)^+$.

b) 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo



Una mezcla de 5-cloro-4-(1-etil-1H-pirazol-5-il)-2-furanocarboxilato de metilo (800 mg, 3,14 mmol) y NCS (600 mg, 4,49 mmol) en THF (5 ml) se calentó a 70ºC en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 10-20%/Hexano), produciendo el compuesto del título (710 mg, 78%) en forma de un sólido de color blanco: LC-MS (ES) m/z 289 $(M+H)^+$.

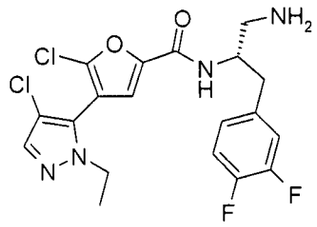
c) 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-2-furanocarboxamida



A una solución de 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxilato de metilo (480 mg, 1,66 mmol) en THF/H_2O (5 ml/1 ml) se le añadió KOH (460 mg, 8,20 mmol). La mezcla de reacción se calentó a 58ºC durante 4 h. Después de que la mezcla se concentrara y se diluyera con H_2O (2 ml), el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (10 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar un ácido bruto (420 mg, 92%), que se usó directamente sin purificación adicional: LC-MS (ES) m/z 275 $(M+H)^+$.

Al ácido anterior (400 mg) en DCM (5 ml) a 25ºC se le añadió en una porción PyBrOP (881 mg, 1,89 mmol), seguido de la adición de DIPEA (1,5 ml, 8,59 mmol). Después de 10 min, se añadió 2-[(2S)-2-amino-3-(3,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (506 mg, 1,60 mmol). Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 30-50%/Hexano), produciendo el compuesto del título (655 mg, 79%) en forma de un sólido de color blanco: LC-MS (ES) m/z 573 $(M+H)^+$.

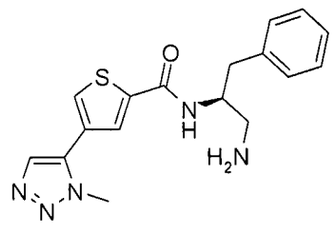
d) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida



A TA, se añadió NH_2NH_2 (0,5 ml, 15,93 mmol) a una solución de 5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-2-furanocarboxamida (610 mg, 1,06 mmol) en MeOH (5 ml). Después de 10 h, el disolvente se retiró al vacío. El residuo resultante se recogió en DCM (20 ml) y se lavó con H_2O (20 ml x 3).

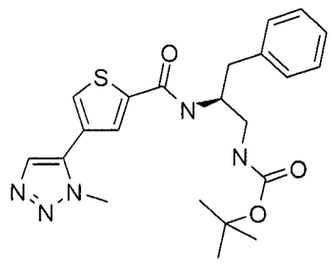
A la solución en DCM se le añadió HCl (al 36%, 10 ml, 120 mmol). Después de 1 h, la fase acuosa se separó y se lavó con DCM (30 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (410 mg, 87%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 443 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 7,61 (s, 1H), 7,36 (s, 1H), 7,29-7,10 (m, 3H), 4,57 (m, 1H), 4,09 (c, J = 7,3 Hz, 2H), 3,27-3,23 (m, 1H), 3,20-3,14 (m, 1H), 3,06-3,01 (m, 1H), 2,97-2,92 (m, 1H) y 1,36 (t, J = 7,3 Hz, 3H).

Ejemplo 260



Preparación de N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

a) [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo

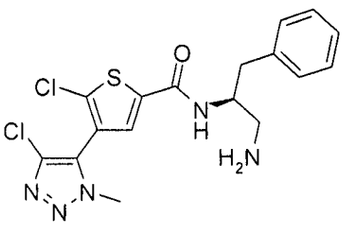


Una mezcla de ((2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (preparado de acuerdo con la Preparación 22 con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(2,4-diclorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2S)-2-amino-3-fenilpropil]-1H-isoindolo-1,3(2H)-diona) (236 mg, 0,537 mmol), 1-metil-5-(tributilestannanil)-1*H*-1,2,3-triazol (200 mg, 0,537 mmol) (preparado de acuerdo con la patente IPN WO97/01553), $Pd(PPh_3)_2Cl_2$ (37,7 mg, 0,054 mmol), TRIETILAMINA (74,9 µl, 0,537 mmol) y tolueno (3 ml) se desgasificó con N_2 y se cerró herméticamente. La mezcla de reacción se calentó a 110ºC durante 4 h. El análisis por LC/MS mostró que la reacción se había completado. La mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 70% en hexano) para dar el producto del título (120 mg, 51%) LCMS (ES) m/z = 442,2 (M+H)

b) *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

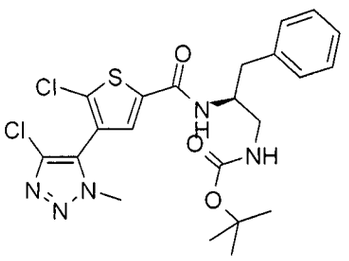
Una solución de [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (60 mg, 0,14 mmol) en TFA-DCM (4 ml, 1:3) se agitó a ta durante 1 h. El análisis por LCMS mostró que la reacción se había completado. La mezcla de reacción se concentró y el residuo se purificó por HPLC de fase inversa (acetonitrilo al 5%-65% en agua con TFA al 0,1%) para dar 42,2 mg (67%) de la sal TFA en forma de un sólido de color blanco. LCMS (ES) m/z 342,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,06 (d, J = 1,52 Hz, 1H), 7,87-7,91 (m, 2H), 7,34-7,21 (m, 5H), 4,55 (m, 1H), 4,19 (s, 3H), 3,30-3,21 (m, 1H), 3,09-3,18 (m, 1H), 3,01 (d, J = 7,6 Hz, 2H)

Ejemplo 261



Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

a) [(2*S*)-2-({[5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



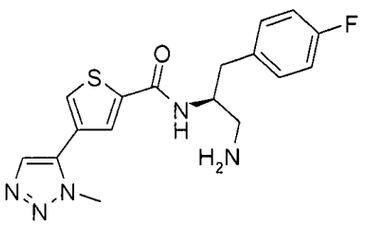
A una solución de [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (70 mg, 0,16 mmol) en 2 ml de DMF se le añadió NCS (42,3 mg, 0,32 mmol). La mezcla de reacción se calentó a 50°C durante 2 h y después se diluyó con 50 ml de EtOAc. La capa orgánica se lavó con H_2O y se concentró para dar el producto del título en forma de una mezcla bruta, que se usó en la siguiente etapa sin purificación. LCMS (ES) m/z = 510,2 (M+H)

b) *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

Una solución de [(2*S*)-2-({[5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (en bruto de la etapa a) en TFA-DCM (4 ml, 1:3) se agitó a ta durante 1 h. La mezcla de reacción se concentró y el residuo se purificó por HPLC de fase inversa (acetonitrilo al 5%-

65% en agua con TFA al 0,1%) para dar 10 mg (12% en dos etapas) de un sólido de color blanco en forma de la sal TFA. LCMS (ES) m/z 410,0/412,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,62 (s, 1H), 7,32-7,25 (m, 5H), 4,55 (m, 1H), 4,02 (s, 3H), 3,21 (m, 1H), 3,10 (m, 1H), 2,98 (d, 2H).

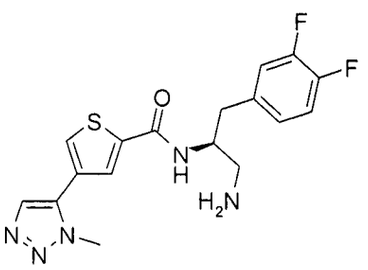
Ejemplo 262



Preparación de N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

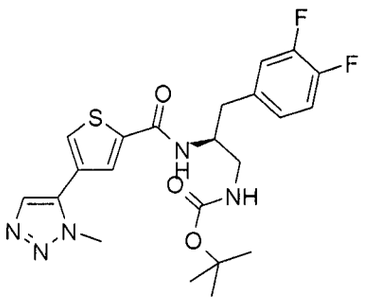
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 260, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-fluorofenil)propil]carbamato de 1,1-dimetiletilo (123 mg, 0,27 mmol). LCMS (ES) m/z 360,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,05 (d, J = 1,6 Hz, 1H), 7,89-7,91 (m, 2H), 7,33-7,30 (m, 2H, 7,06-7,02 (m, 2H), 4,55 (m, 1H), 4,20 (s, 3H), 3,23 (m, 1H), 3,17 (m, 1H), 2,99 (m, 2H).

Ejemplo 263



Preparación de N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

a) [(2*S*)-3-(3,4-difluorofenil)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)propil]carbamato de 1,1-dimetiletilo

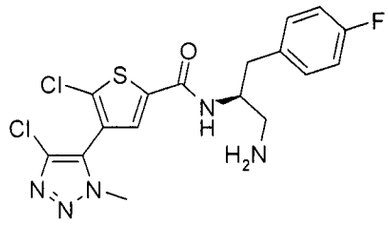


Una solución de [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo (50 mg, 0,11 mmol), 1-metil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1*H*-1,2,3-triazol (44 mg, 0,21 mmol), Na_2CO_3 (2 N, 0,1 ml) y $PddppfCl_2$ (8,6 mg, 0,01 mmol) en 3 ml de 1,4-dioxano se irradió en un reactor de MO a 150ºC durante 20 min. La mezcla de reacción bruta se purificó por cromatografía en columna (sílice, EtOAc al 70% en hexano) para dar el producto del título (29 mg, 46%): LCMS (ES) m/z = 478,2 (M+H).

b) *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó de acuerdo con el Ejemplo 260 b) con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-3-(3,4-difluorofenil)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)propil] carbamato de 1,1-dimetiletilo (29 mg, 0,06 mmol). LCMS (ES) m/z 378,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,07 (d, J = 1,6 Hz, 1H), 7,88-7,91 (m, 2H), 7,23-7,09 (m, 3H), 4,55 (m, 1H), 4,20 (s, 3H), 3,24 (m, 1H), 3,15 (m, 1H), 2,98 (m, 2H).

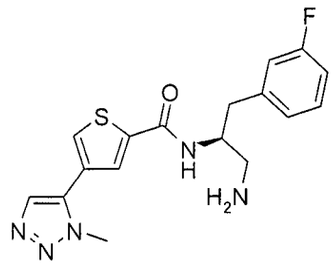
Ejemplo 264



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-(4-fluorofenil)propil]carbamato de 1,1-dimetiletilo (68 mg, 0,15 mmol). LCMS (ES) m/z 428,0/430,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,66 (s, 1H), 7,30 (m, 2H), 7,04 (m, 2H), 4,55 (m, 1H), 4,02 (s, 3H, 3,21-3,10 (m, 2H), 2,98 (m, 2H).

Ejemplo 265

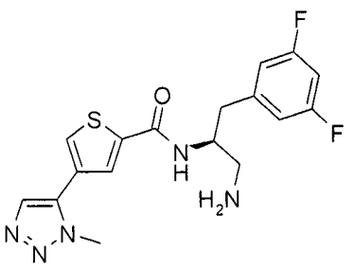


Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 263, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-

tienil)carbonil]amino}-3-(3-fluorofenil)propil]carbamato de 1,1-dimetiletilo (300 mg, 0,66 mmol). LCMS (ES) m/z 360,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,06 (d, J = 1,6 Hz, 1H), 7,90 (m, 2H), 7,33-7,30 (m, 1H), 7,13-7,09 (m, 2H), 6,98-6,95 (m, 1H), 4,55 (m, 1H), 4,19 (s, 3H), 3,24 (m, 1H), 3,17 (m, 1H), 3,04-2,99 (m, 2H).

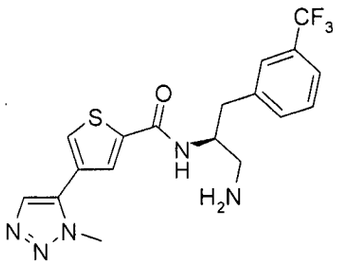
Ejemplo 266



Preparación de *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 263, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,5-difluorofenil)propil]carbamato de 1,1-dimetiletilo (300 mg, 0,66 mmol). LCMS (ES) m/z 378,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,06 (d, J = 1,6 Hz, 1H), 7,91 (m, 2H), 6,96-6,93 (m, 2H), 6,84-6,83 (m, 1H), 4,55 (m, 1H), 4,19 (s, 3H), 3,24 (m, 1H), 3,19 (m, 1H), 3,05-2,98 (m, 2H).

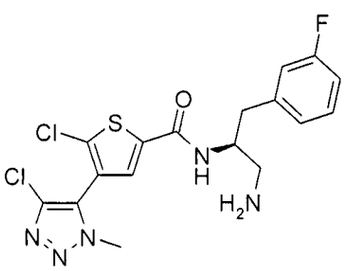
Ejemplo 267



Preparación de *N*-{(1*S*)-2-amino-1-[(3-trifluorometilfenil)metil]etil}-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 263, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3-(trifluorometil)fenil)propil]carbamato de 1,1-dimetiletilo (500 mg, 0,99 mmol). LCMS (ES) m/z 410,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,06 (d, J = 1,2 Hz, 1H), 7,97 (s, 1H), 7,91 (s, 1H), 7,72 (d, J = 1,2 Hz, 1H) 7,54 (m, 2H), 7,44 (m, 1H), 4,55 (m, 1H), 4,21 (s, 3H), 3,30-3,10 (m, 4H).

Ejemplo 268

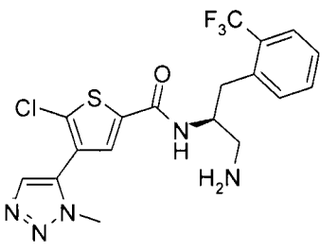


Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se

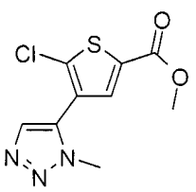
sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-(3-fluorofenil)propil]carbamato de 1,1-dimetiletilo (50 mg, 0,11 mmol). LCMS (ES) m/z 428,0/430,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,63 (s, 1H), 7,33 (m, 1H), 7,12-7,07 (m, 3H), 4,55 (m, 1H), 4,02 (s, 3H), 3,23-2,98 (m, 4H).

Ejemplo 269



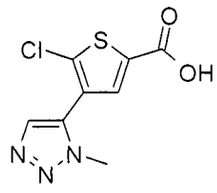
Preparación de N-{(1S)-2-amino-1-[(2-(trifluorometil)fenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

a) 5-cloro-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxilato de metilo



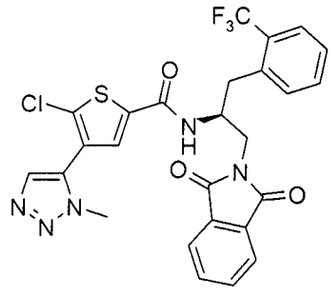
Una mezcla de 1-metil-5-(tributilestannanil)-1*H*-1,2,3-triazol (2,0 g, 5,37 mmol), 4-bromo-5-cloro-2-tiofenocarboxilato de metilo (1,25 g, 4,9 mmol), $Pd(PPh_3)_2Cl_2$ (171 mg, 0,244 mmol), TRIETILAMINA (0,68 ml, 4,89 mmol) y tolueno (3 ml) se calentó a 110°C durante 4 h en una atmósfera de N_2. La mezcla de reacción se purificó por cromatografía en columna (sílice, EtOAc al 50%-70% en hexano) para dar el compuesto del título en forma de un sólido de color blanco (400 mg, 32%): LCMS (ES) m/z 258,2 $(M+H)^+$.

b) ácido 5-cloro-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico



Una solución de 5-cloro-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxilato de metilo (400 mg, 1,55 mmol) y LiOH 1 N (2,0 ml, 2,0 mmol) en THF (6 ml) se agitó a ta durante una noche. Después de la retirada del THF, el residuo se diluyó con 10 ml de H_2O y se lavó con DCM (10 ml x 2). La capa acuosa se acidificó a un valor de pH de 3 con HCl 1 N y después se extrajo con EtOAc (30 ml x 4). Las capas orgánicas se combinaron y se concentraron para dar 370 mg del compuesto del título en forma de un sólido de color blanco. LCMS (ES) m/z 244,0 $(M+H)^+$

c) 5-Cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

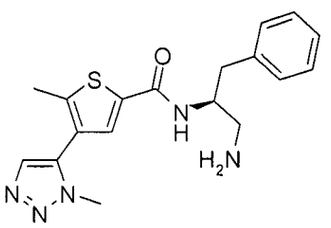


Una solución de ácido 5-cloro-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico (370 mg, 1,52 mmol), 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona (de la Preparación 6, 529 mg, 1,52 mmol), PyBrop (708 mg, 1,52 mmol) y DIPEA (2,65 ml, 15,2 mmol) en 20 ml de DCM se agitó a ta durante 2 h. La mezcla de reacción se diluyó con 50 ml de DCM y se lavó con H_2O, HCl 0,1 N y salmuera. La capa orgánica se concentró y el residuo se purificó por cromatografía en columna (sílice, EtOAc al 50%-70% en hexano) para dar el compuesto del título en forma de un sólido de color blanco (700 mg, 80%): LCMS (ES) m/z 574,0 $(M+H)^+$.

d) N-{(1S)-2-amino-1-[(2-(trifluorometil)fenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

Una solución de 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida (700 mg, 1,22 mmol) e hidrazina (0,19 ml, 6,1 mmol) en 5 ml de MeOH se agitó a ta durante una noche, se diluyó con 200 ml de H_2O y se extrajo con DCM (100 ml x 2). Las capas orgánicas combinadas se concentraron y el sólido resultante se disolvió en HCl 6 N (50 ml). La capa acuosa se lavó con DCM (50 ml x 2). Las capas orgánicas se desecharon y la solución acuosa restante se concentró para dar el producto en forma de una sal HCl (490 mg, 75%): LCMS (ES) m/z 444,0 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,10 (m, 1H), 7,92 (m, 1H), 7,73 (m, 1H), 7,57 (m, 1H), 7,44 (m, 1H), 4,65 (m, 1H), 4,17 (s, 3H), 3,25-3,11 (m, 4H).

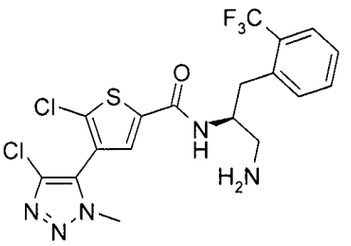
Ejemplo 270:



Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-metil-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 269, con la excepción de que se sustituyó 4-bromo-5-cloro-2-tiofenocarboxilato de metilo por 4-bromo-5-metil-2-tiofenocarboxilato de metilo (de la Preparación 10) y 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-{(2*S*)-2-amino-3-fenilpropil}-1*H*-isoindolo-1,3(2*H*)-diona (preparación 5). LCMS (ES) m/z 356,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,60 (s, 1H), 8,01 (s, 1H), 7,34-7,21 (m, 5H), 4,55 (m, 1H), 4,26 (s, 3H), 3,25 (m, 2H), 3,03 (m, 2H), 2,21 (s, 3H).

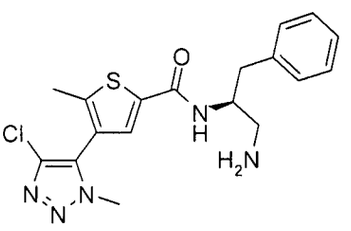
Ejemplo 271



Preparación de N-{(1S)-2-amino-1-[(2-(trifluorometil)fenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por N-{(1S)-2-amino-1-[(2-(trifluorometil)fenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida (120 mg, 0,27 mmol). LCMS (ES) m/z 478,0/ 480,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,79 (s, 1H), 7,73 (d, J = 7,6 Hz, 1H), 7,56 (m, 2H), 7,45 (m, 1H), 4,65 (m, 1H), 4,05 (s, 3H), 3,29-3,10 (m, 4H).

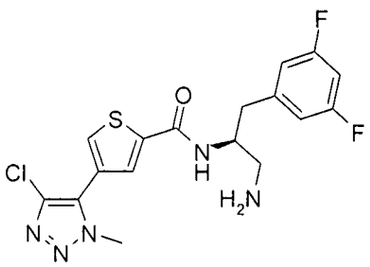
Ejemplo 272



Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-5-metil-2-tiofenocarboxamida

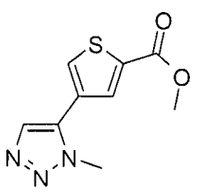
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[5-metil-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (preparado en el Ejemplo 270): LCMS (ES) m/z 390,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 7,72 (s, 1H), 7,31-7,22 (m, 5H), 4,55 (m, 1H), 3,99 (s, 3H), 3,19 (m, 2H), 3,02 (m, 2H), 2,41 (s, 3H).

Ejemplo 273



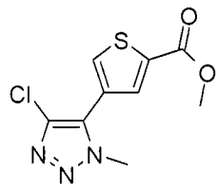
Preparación de *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

a) 4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxilato de metilo



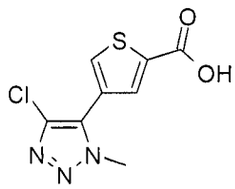
El compuesto del título se preparó de acuerdo con el procedimiento del Ejemplo 269 a), con la excepción de que se sustituyó 4-bromo-5-cloro-2-tiofenocarboxilato de metilo por 4-bromo-2-tiofenocarboxilato de metilo. LCMS (ES) m/z 224,0 $(M+H)^+$.

b) 4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxilato de metilo



Una solución de 4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxilato de metilo (500 mg, 2,24 mmol) y NCS (1196 mg, 8,96 mmol) en N,N-dimetilformamida (DMF) (10 ml) se calentó a 50ºC durante 2 h. La mezcla de reacción se diluyó con 50 ml de EtOAc. La capa orgánica se lavó con H_2O (50 ml x 2) y salmuera (50 ml) y después se concentró para dar 460 mg de una mezcla bruta, que se usó en la siguiente etapa sin separación adicional. LCMS (ES) m/z 258,0 $(M+H)^+$.

c) ácido 4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico



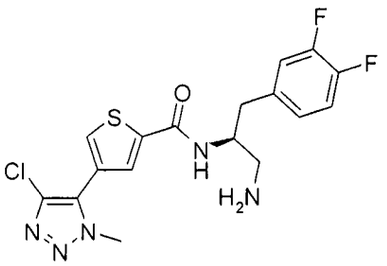
El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 269 b), con la excepción de que se sustituyó 4-(1-metil-1*H*-1,2,3-triazol-5-il)-5-cloro-2-tiofenocarboxilato de metilo por 4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxilato de metilo. LCMS (ES) m/z 244,0 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 269 c-d), con la excepción de que se sustituyó ácido 4-(1-metil-1*H*-1,2,3-triazol-5-il)-5-cloro-2-tiofenocarboxílico por ácido 4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico y se sustituyó 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona. LCMS (ES) m/z 412,0/414,0 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-

*d*4) ppm 8,13 (m, 1H), 8,06 (m, 1H), 6,97 (m, 2H), 6,82 (m, 1H), 4,55 (m, 1H), 4,16 (s, 3H), 3,26 (m, 2H), 3,04 (m, 2H).

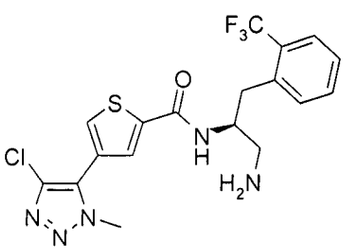
Ejemplo 274



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 273, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(3,4-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (82 mg, 0,15 mmol). LCMS (ES) m/z 412,0/414,0 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,12 (d, J = 1 Hz, 1H), 8,05 (d, J = 1 Hz, 1H) 7,30-7,10 (m, 3H), 4,55 (m, 1H), 4,16 (s, 3H), 3,26 (m, 2H), 2,99 (m, 2H).

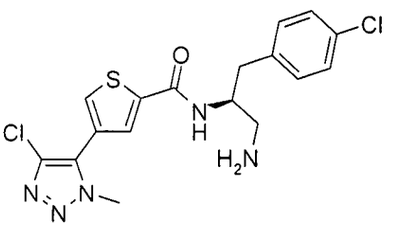
Ejemplo 275



Preparación de *N*-{(1*S*)-2-amino-1-[(2-(trifluorometil)fenil)metil]etil}-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 274, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(2-(trifluorometil)fenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (130 mg, 0,23 mmol). LCMS (ES) m/z 444,0/446,0 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,13 (d, J = 1 Hz, 1H), 8,09 (d, J = 1 Hz, 1H), 7,72 (m, 1H), 7,56 (m, 2H), 7,43 (m, 1H), 4,60 (m, 1H), 4,17 (s, 3H), 3,26-3,15 (m, 4H).

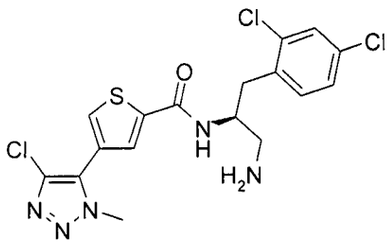
Ejemplo 276



Preparación de *N*-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 273, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(4-clorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (73 mg, 0,14 mmol). LCMS (ES) m/z 410,0/412,0 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,12 (d, J = 1 Hz, 1H), 8,03 (d, J = 1 Hz, 1H), 7,31 (m, 4H), 4,55 (m, 1H), 4,15 (s, 3H), 3,26 (m, 2H), 3,05 (m, 2H).

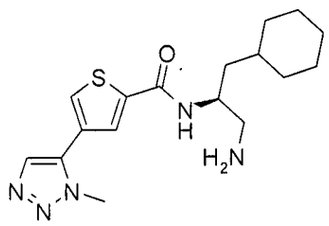
Ejemplo 277



Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó siguiendo el procedimiento del Ejemplo 273, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(2,4-diclorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona (67 mg, 0,12 mmol). LCMS (ES) m/z 444,0/448,0 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,12 (d, J = 1 Hz, 1H), 8,03 (d, J = 1 Hz, 1H), 7,49 (d, 1H), 7,38 (d, 1H), 7,25 (m, 1H), 4,60 (m, 1H), 4,16 (s, 3H), 3,30-3,09 (m, 4H).

Ejemplo 278

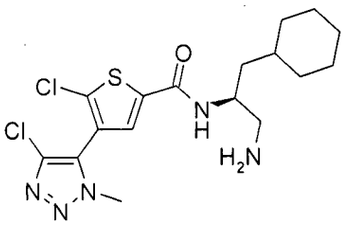


Preparación de *N*-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 263, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(ciclohexil)propil]carbamato de 1,1-dimetiletilo (300 mg, 0,67 mmol). LCMS (ES) m/z 348,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,09

(d, J = 1 Hz, 1H), 8,03 (d, J = 1 Hz, 1H), 7,91 (s, 1H), 4,48 (m, 1H), 4,22 (s, 3H), 3,20 (m, 1H), 3,05 (m, 1H), 2,00-0,95 (m, 13H).

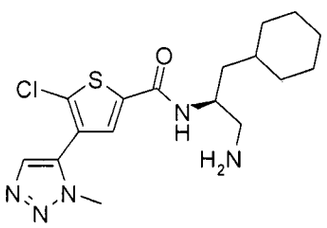
Ejemplo 279



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-ciclohexilpropil]carbamato de 1,1-dimetiletilo (50 mg, 0,11 mmol). LCMS (ES) m/z 416,0/418,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,74 (s, 1H), 4,48 (m, 1H), 4,04 (s, 3H), 3,40-2,95 (m, 2H), 1,90-0,95 (m, 13H).

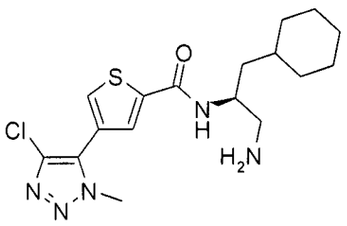
Ejemplo 280



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 269, con la excepción de que se sustituyó 2-{(2*S*)-2-amino-3-[3-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-ciclohexilpropil]-1*H*-isoindolo-1,3(2*H*)-diona. LCMS (ES) m/z 382,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 7,93 (s, 1H), 7,81 (m, 1H), 4,43 (m, 1H), 4,10 (s, 3H), 3,17 (m, 1H), 3,05 (m, 1H), 2,00-0,90 (m, 13H).

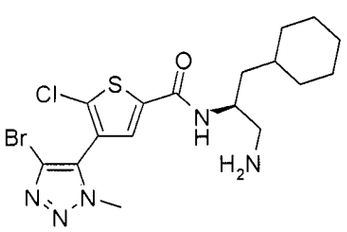
Ejemplo 281



Preparación de *N*-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento de 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-ciclohexilpropil]carbamato de 1,1-dimetiletilo (100 mg, 0,22 mmol) y la cantidad de NCS se redujo hasta 1 equiv. LCMS (ES) m/z 382,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,15 (d, J = 1 Hz, 1H), 8,08 (d, J = 1 Hz, 1H), 4,45 (m, 1H), 4,16 (s, 3H), 3,14 (m, 1H), 3,05 (m, 1H), 2,00-0,90 (m, 13H).

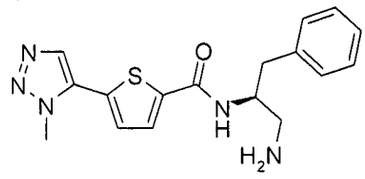
Ejemplo 282



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-bromo-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

Una solución de [(2*S*)-2-({[5-cloro-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-ciclohexilpropil]carbamato de 1,1-dimetiletilo (140 mg, 0,29 mmol, preparado en el Ejemplo 280) y NBS (103 mg, 0,58 mmol) en 2 ml de DMF se calentó a 100°C durante 2 horas. La mezcla de reacción se purificó por HPLC de fase inversa (acetonitrilo al 5-65% en H_2O con TFA al 1%) para dar el compuesto del título 14,1 mg (8%) en forma de un sólido de color blanco. LCMS (ES) m/z 462,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,75 (s, 1H), 4,43 (m, 1H), 4,05 (s, 3H), 3,17 (m, 1H), 3,05 (m, 1H), 2,00-0,90 (m, 13H).

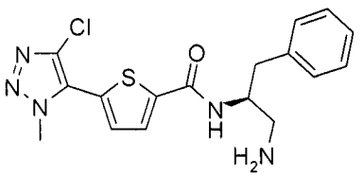
Ejemplo 283



Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 260, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(5-bromo-2-tienil)carbonil]amino}-3-fenilpropil]carbamato de 1,1-dimetiletilo (270 mg, 0,62 mmol). LCMS (ES) m/z 342,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,96 (s, 1H), 7,75 (d, J = 3,6 Hz, 1H), 7,47 (d, J = 3,6 Hz, 1H), 7,31-7,22 (m, 5H), 4,55 (m, 1H), 4,21 (s, 3H), 3,20 (m, 2H) 2,99 (m, 2H).

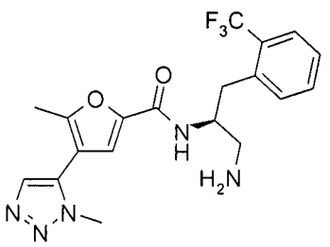
Ejemplo 284



Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[5-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (68 mg, 0,15 mmol). LCMS (ES) m/z 376,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 7,82 (m, 1H), 7,55 (d, J = 3,6 Hz, 1H), 7,47 (d, J = 3,6 Hz, 1H), 7,32-7,23 (m, 5H), 4,55 (m, 1H), 4,19 (s, 3H), 3,20 (m, 2H), 3,02 (m, 2H).

Ejemplo 285

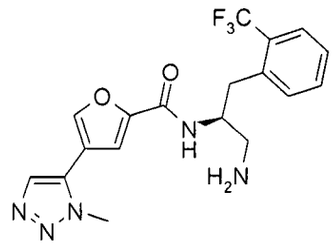


Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 269, con la excepción de que se sustituyó 4-bromo-5-cloro-2-tiofenocarboxilato de metilo por 4-bromo-5-metil-2-furanocarboxilato de metilo (ref. Bach, T.; Kruger, L. *Synlett* **1998**, 1185-1186). LCMS (ES) m/z 408,2 $(M+H)^+$, ^{1}H RMN (400 MHz, METANOL-*d*4) ppm 8,09

(s, 1H), 7,71 (m, 1H), 7,55 (m, 2H), 7,43 (m, 2H), 4,68 (m, 1H), 4,13 (s, 3H), 3,25-3,15 (m, 4H), 2,48 (s, 3H).

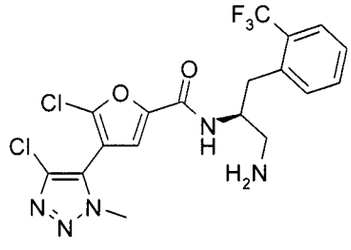
Ejemplo 286



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 260, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-furanil)carbonil]amino}-3-(2-(trifluorometil)fenil)propil]carbamato de 1,1-dimetiletilo (200 mg, 0,4 mmol). LCMS (ES) m/z 394,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,23 (s, 1H), 7,93 (s, 1H), 7,71 (d, 1H), 7,54 (m, 2H), 7,43 (m, 2H), 4,75 (m, 1H), 4,18 (s, 3H), 3,30-3,10 (m, 4H).

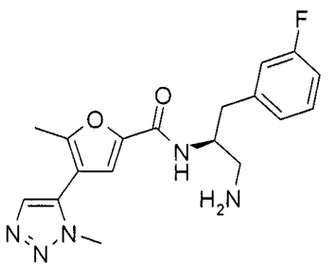
Ejemplo 287



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-furanil]carbonil}amino)-3-(2-(trifluorometil)fenil)propil]carbamato de 1,1-dimetiletilo (90 mg, 0,18 mmol). LCMS (ES) m/z 462,0/464,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,73 (m, 1H), 7,56 (m, 2H), 7,45 (m, 1H), 7,40 (s, 1H), 4,75 (m, 1H), 4,05 (s, 3H), 3,30-3,10 (m, 4H).

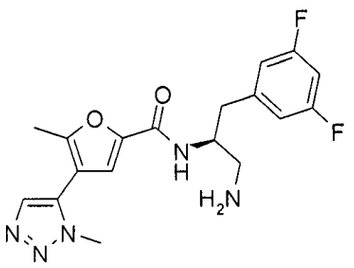
Ejemplo 288



Preparación de *N*-((1*S*)-2-amino-1-{[3-fluorofenil]metil}etil)-5-metil-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 269, con la excepción de que se sustituyó 4-bromo-5-cloro-2-tiofenocarboxilato de metilo por 4-bromo-5-metil-2-furanocarboxilato de metilo y 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-{(2*S*)-2-amino-3-[3-fluorofenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona. LCMS (ES) m/z 358,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,47 (s, 1H), 7,44 (s, 1H), 7,35 (m, 1H), 7,15 (m, 2H), 6,96 (m, 1H), 4,65 (m, 1H), 4,22 (s, 3H), 3,25 (m, 2H), 3,04 (m, 2H), 2,49 (s, 3H).

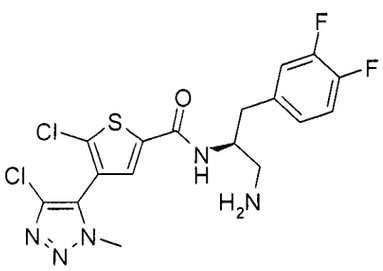
Ejemplo 289



Preparación de *N*-((1*S*)-2-amino-1-{[3,5-difluorofenil]metil}etil)-5-metil-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 269, con la excepción de que se sustituyó 4-bromo-5-cloro-2-tiofenocarboxilato de metilo por 4-bromo-5-metil-2-furanocarboxilato de metilo y 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-{(2*S*)-2-amino-3-[3,5-difluorofenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona. LCMS (ES) m/z 376,2 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 8,30 (s, 1H), 7,43 (s, 1H), 6,95 (m, 2H), 6,82 (m, 1H), 4,53 (m, 1H), 4,18 (s, 3H), 3,25 (m, 2H), 3,07 (m, 2H), 2,48 (s, 3H).

Ejemplo 290

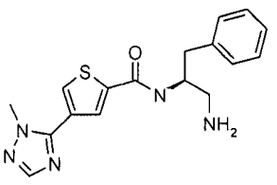


Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 261, con la excepción de que se sustituyó [(2*S*)-2-({[4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tienil]carbonil}amino)-3-

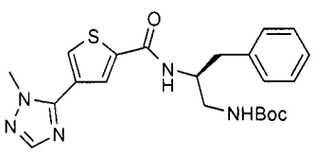
fenilpropil]cabamato de 1,1-dimetiletilo por *N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida (preparada de acuerdo con el Ejemplo 263) y siguiendo el Ejemplo 269 para la desprotección. LCMS (ES) m/z 446,0/448,0 $(M+H)^+$, ^1H RMN (400 MHz, METANOL-*d*4) ppm 7,88 (s, 1H), 7,20-7,15 (m, 3H), 4,53 (m, 1H), 4,05 (s, 3H), 3,23 (m, 2H), 3,00 (m, 2H).

Ejemplo 291



Preparación de *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

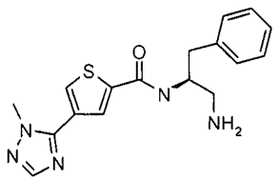
a) [(2S)-2-({[4-(1-metil-1H-1,2,4-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo



Una suspensión de ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (preparado de acuerdo con la preparación 22 con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(2,4-diclorofenil)propil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,455 mmol) por 2-[(2S)-2-amino-3-fenilpropil]-1H-isoindolo-1,3(2H)-diona), 5,5,5',5'-tetrametil-2,2'-bi-1,3,2-dioxaborinano (123 mg, 0,546 mmol), acetato potásico (134 mg, 1,366 mmol) y $PdCl_2(dppf)_2$ (16,7 mg, 0,023 mmol) en THF seco (3 ml) se cargó en un tubo cerrado herméticamente y se calentó a 80°C durante una hora. Después, se añadieron 5-yodo-1-metil-1H-1,2,4-triazol (114 mg, 0,546 mmol), carbonato sódico 2 M (0,34 ml, 0,683 mmol) y $Pd(Ph_3P)_4$ (26,3 mg, 0,023 mmol). La mezcla se calentó a 85°C durante 2 horas. El

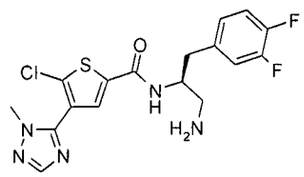
disolvente se retiró y el residuo se purificó por biotage (70% de H/E) para dar el producto del título (120 mg, 60%)

b) *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida



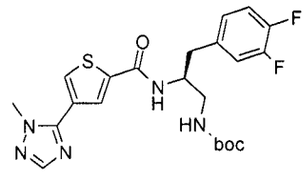
Se añadió TFA (1 ml) a una solución de [(2S)-2-({[4-(1-metil-1H-1,2,4-triazol-5-il)-2-tienil]carbonil}amino)-3-fenilpropil]carbamato de 1,1-dimetiletilo (100 mg, 0,226 mmol) en DCM (5 ml). La reacción se agitó a TA durante 30 min. El disolvente se retiró y el residuo se purificó por HPLC de fase inversa (10% org ~ 60% org) para dar el compuesto del título en forma de un sólido de color blanco (90 mg, 87%). LC-MS (ES) m/z 342,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,23 (s, 1H), 8,03 (m, 2H), 7,22-7,31 (m, 5H), 4,60 (m, 1H), 4,08 (s, 3H), 3,10-3,20 (m, 2H), 3,00 (m, 2H).

Ejemplo 292



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

a) [(2*S*)-3-(3,4-difluorofenil)-2-({[4-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tienil]carbonil}amino)propil]carbamato de 1,1-dimetiletilo

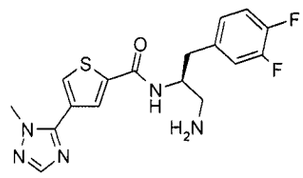


Este intermedio se preparó de acuerdo con el procedimiento del Ejemplo 291 a) con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z = 478,2 $(M+H)^+$

b) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

Una solución de [(2*S*)-3-(3,4-difluorofenil)-2-({[4-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tienil]carbonil}amino)propil]carbamato de 1,1-dimetiletilo (279 mg, 0,497 mmol) y NCS (133 mg, 0,993 mmol) en N,N-dimetilformamida (DMF) (3 ml) se calentó a 110°C durante 1 h. La mezcla de reacción bruta se concentró y el residuo se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (9:1:1 de DCM:MeOH:NH_4OH) para dar el producto en forma de una base libre, que se trató con 0,13 ml de HCl ac. 2 N (2 equiv.) para dar 75 mg de la sal HCl en forma de un sólido de color blanquecino. LC-MS (ES) m/z = 412 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 8,80 (s, 1H), 8,18 (s, 1H), 7,3-7,1 (m, 3H), 4,54 (m, 1H), 4,11 (s, 3H), 3,26 (d, J = 7 Hz, 2H), 3,03 (d, J = 8 Hz, 2H).

Ejemplo 293

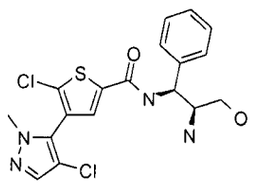


Preparación de *N*-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanquecino de acuerdo con el procedimiento del Ejemplo 291 con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo. El producto final se purificó por cromatografía en columna ultrarrápida sobre gel de sílice (9:1:1 de

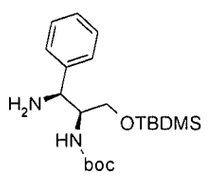
DCM:MeOH:NH_4OH) para dar una base libre, que se trató con una solución ac. 2 N de HCl para dar la sal HCl. LC-MS (ES) m/z = 378 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 8,78 (s, 1H), 8,50 (d, J = 2 Hz, 1H), 8,36 (d, J = 2 Hz, 1H), 7,3-7,1 (m, 3H), 4,57 (m, 1H), 4,23 (s, 3H), 3,27 (d, J = 8 Hz, 2H), 3,04 (d, J = 8 Hz, 2H).

Ejemplo 294



Preparación de *N*-[(1*S*,2*S*)-2-amino-3-hidroxi-1-fenilpropil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

a) [(1*S*,2*S*)-2-amino-1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2-feniletil]carbamato de 1,1-dimetiletilo

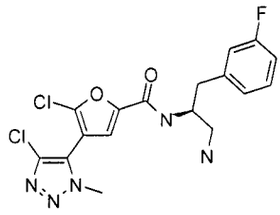


El compuesto del título se preparó de acuerdo con la Preparación 1 con la excepción de que se sustituyó (2-hidroxi-2-feniletil)carbamato de 1,1-dimetiletilo por [(1*R*,2*R*)-1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2-hidroxi-2-feniletil]carbamato de 1,1-dimetiletilo (ref. Veeresa, G.; Datta, Apurba. *Stereoselective synthesis of chloramphenicol from D-serine.* Tetrahedron Letters (**1998**), 39(46), 8503-8504).

b) *N*-[(1*S*,2*S*)-2-amino-3-hidroxi-1-fenilpropil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

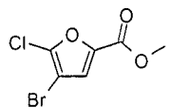
Este intermedio se preparó de acuerdo con los procedimientos del Ejemplo 261, con la excepción de que se sustituyó (2-amino-2-feniletil)carbamato de 1,1-dimetiletilo por [(1*S*,2*S*)-2-amino-1-({[(1,1-dimetiletil)(dimetil)silil]oxi}metil)-2-feniletil]carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z = 425,0/427,0 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 7,86 (s, 1H), 7,59 (s, 1H), 7,56-7,38 (m, 5H), 5,50 (m, 1H), 3,91-3,84 (m, 3H).

Ejemplo 295



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

a) 4-bromo-5-cloro-2-furanocarboxilato de metilo



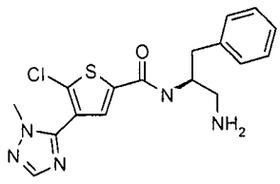
Se añadió gota a gota cloruro de isopropilmagnesio (1,20 ml, 2,40 mmol) a una solución de 4,5-dibromo-2-furanocarboxilato de metilo (568 mg, 2,0 mmol) en tetrahidrofurano (THF) (16 ml) a 0°C. La mezcla resultante se agitó a esta temperatura durante 30 min y después se enfrió a -78°C. Se añadió gota a gota una solución de hexilcloroetano (568 mg, 2,401 mmol) en THF (1 ml) y la mezcla resultante se agitó a esta temperatura durante 1 h. La reacción se interrumpió mediante la adición de NH_4Cl (ac. sat.) y la mezcla resultante se agitó a ta durante una noche. Se añadieron éter y agua y la capa acuosa se desechó. La capa orgánica se lavó con salmuera, se secó (Na_2SO_4) y se concentró para dar 0,34 g del producto que contenía su éster isopropílico.

b) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida

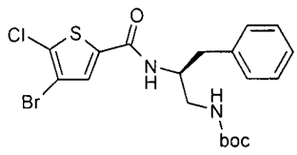
El compuesto del título se preparó de acuerdo con el procedimiento del Ejemplo 273, con la excepción de que se sustituyó 4-bromo-2-tiofenocarboxilato de metilo por 4-bromo-5-cloro-2-furanocarboxilato de metilo y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona. El producto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z = 412,0/414,0 $(M+H)^+$, ^1H RMN (CD_3OD, 400 MHz) 7,44 (s,

1H), 7,33 (m, 1H), 7,14-7,07 (m, 2H), 6,98 (m, 1H), 4,55 (m, 1H), 4,05 (s, 3H), 3,25-2,98 (m, 4H).

Ejemplo 296



Preparación de N-[(1S)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida



a) ((2*S*)-2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo

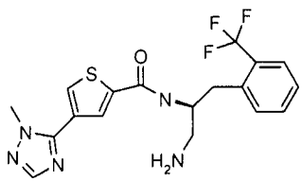
Una solución de ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo (preparado de acuerdo con la Preparación 22), con la excepción de que se sustituyó 2-[(2S)-2-amino-3-(2,4-diclorofenil)propil]-1H-isoindolo-1,3(2H)-diona (200 mg, 0,455 mmol) por 2-[(2S)-2-amino-3-fenilpropil]-1H-isoindolo-1,3(2H)-diona) y NCS (61 mg, 0,455 mmol) en DMF (3 ml) se calentó a 50°C en un tubo cerrado herméticamente durante 2 horas. El disolvente se retiró y el residuo se purificó por biotage (Hex al 30%/EtOAc) para dar el producto del título (140 mg, 65%).

b) *N*-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por ((2*S*)-2-{[(4-bromo-5-cloro-2-tienil)carbonil]amino}-3-

fenilpropil)carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z 376,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,12 (s, 1H), 7,74 (s, 1H), 7,31-7,35 (m, 5H), 4,58 (m, 1H), 3,94 (s, 3H), 3,35 (m, 2H), 3,05 (m, 2H).

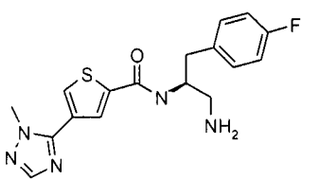
Ejemplo 297



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z 410,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,33 (m, 2H), 7,73 (m, 1H), 7,41-7,56 (m, 4H), 4,70 (m, 1H), 4,13 (s, 3H), 3,36 (m, 2H), 3,18 (m, 2H).

Ejemplo 298

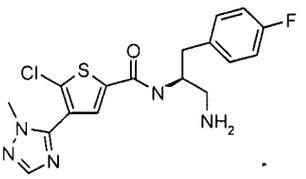


Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-

dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-fluorofenil)propil]carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z 360,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,24 (s, 1H), 8,06 (m, 2H), 7,29-7,34 (m, 2H), 7,01-7,05 (m, 2H), 4,66 (m, 1H), 4,08 (s, 3H), 3,23 (m, 2H), 3,15 (m, 2H).

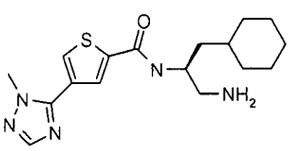
Ejemplo 299



Preparación de *N*-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-fluorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC para dar el compuesto del título en forma de un sólido de color blanco. LC-MS (ES) m/z 394,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,10 (s, 1H), 7,70 (s, 1H), 7,28-7,31 (m, 2H), 7,01-7,06 (m, 2H), 4,56 (m, 1H), 3,92 (s, 3H), 3,21 (m, 2H), 2,96 (m, 2H).

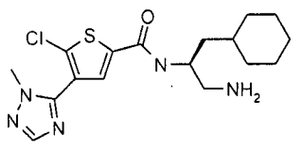
Ejemplo 300



Preparación de *N*-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por ((2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-ciclohexilpropil)carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z 348,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,27 (m, 1H), 8,13 (s, 1H), 8,02 (s, 1H), 4,56 (m, 1H), 4,11 (s, 3H), 3,16 (m, 1H), 3,02 (m, 1H), 1,17-1,95 (m, 13H)

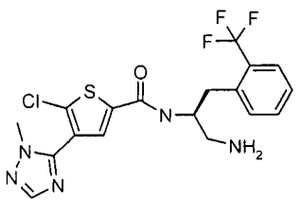
Ejemplo 301



Preparación de N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por ((2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-ciclohexilpropil)carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC para dar el compuesto del título en forma de un sólido de color blanco. LC-MS (ES) m/z 382,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,10 (s, 1H), 7,82 (s, a, 1H), 4,42 (m, 1H), 3,94 (s, 3H), 3,16-3,30 (m, 1H), 2,98-3,10 (m, 1H), 1,06-1,96 (m, 13H)

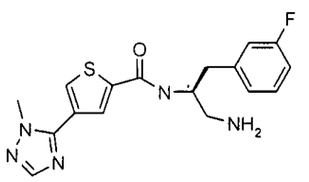
Ejemplo 302



Preparación de N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC para dar el compuesto del título en forma de un sólido de color blanco. LC-MS (ES) m/z 444,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,20 (s, a, 1H), 7,86 (s, a, 1H), 7,71 (m, 1H), 7,42-7,56 (m, 3H), 4,63 (m, 1H), 3,96 (s, 3H), 3,09-3,27 (m, 4H).

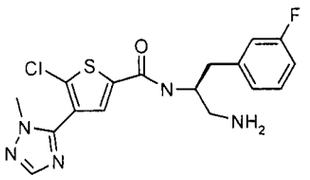
Ejemplo 303



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3-fluorofenil)propil]carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z 360,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,24 (s, 1H), 8,02 (m, 2H), 7,30 (m, 1H) 7,06-7,13 (m, 2H), 6,96 (m, 1H), 4,63 (m, 1H), 4,08 (s, 3H), 3,09-3,27 (m, 4H).

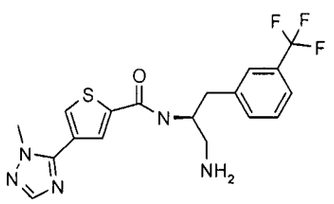
Ejemplo 304



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3-fluorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC para dar el compuesto del título en forma de un sólido de color blanco. LC-MS (ES) m/z 394,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,10 (s, 1H), 7,70 (s, 1H), 7,31 (m, 1H), 6,97-7,11 (m, 3H), 4,52 (m, 1H), 3,92 (s, 3H), 2,96-3,26 (m, 4H)

Ejemplo 305

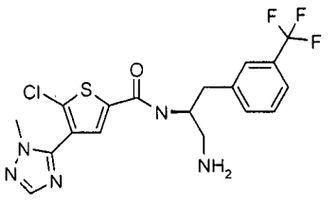


Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-[3-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 410,2 $(M+H)^+$, ^1H RMN

(d_4-MeOH, 400 MHz) 8,81 (s, 1H), 8,51 (d, J = 1 Hz, 1H), 8,39 (d, J = 1 Hz, 1H), 7,64 (m, 2H), 7,50 (m, 2H), 4,66 (m, 1H), 4,23 (s, 3H), 3,30 (m, 2H), 3,15 (m, 2H).

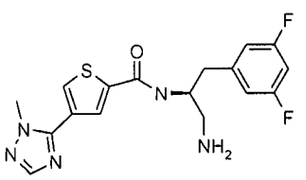
Ejemplo 306



Preparación de *N*-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-[3-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 440,0 $(M+H)^+$, ^{1}H RMN (d_4-MeOH, 400 MHz) 8,53 (s, 1H), 8,02 (s, 1H), 7,50-7,64 (m, 4H), 4,56 (m, 1H), 4,03 (s, 3H), 3,10-3,27 (m, 4H).

Ejemplo 307

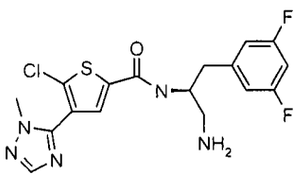


Preparación de *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-

2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,5-difluorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 378,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,68 (s, 1H), 8,47 (d, J = 1 Hz, 1H), 8,35 (d, J = 1 Hz, 1H), 6,96 (m, 2H), 6,80 (m, 1H), 4,60 (m, 1H), 4,21 (s, 3H), 3,28 (m, 2H), 3,08 (m, 2H).

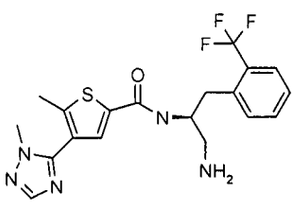
Ejemplo 308



Preparación de N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

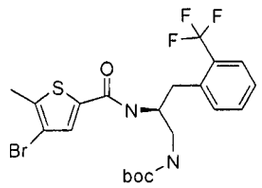
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,5-difluorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 412,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,44 (s, 1H), 7,98 (s, 1H), 6,96 (m, 2H), 6,82 (m, 1H), 4,66 (m, 1H), 4,01 (s, 3H), 3,20-3,25 (m, 2H), 3,02-3,05 (m, 2H).

Ejemplo 309



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

a) {(2*S*)-2-{[(4-bromo-5-metil-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo

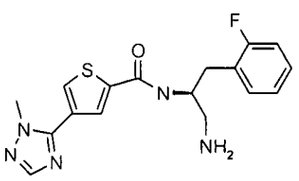


Este intermedio se preparó de acuerdo con la Preparación 22, con la excepción de que se sustituyó ácido 4-bromo-2-tiofenocarboxílico por ácido 4-bromo-5-metil-2-tiofenocarboxílico (Bioorganic & Medicinal Chemistry Letters (2002), 12(3), 491-495) y se sustituyó 2-[(2*S*)-2-amino-3-(2,4-diclorofenil)propil]-1*H*-isoindolo-1,3(2*H*)-diona por 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-isoindolo-1,3(2*H*)-diona.

b) *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-5-metil-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo: El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 424,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,68 (s, 1H), 8,04 (s, 1H), 7,70 (m, 1H), 7,58 (m, 1H), 7,52 (m, 1H), 7,43 (m, 1H), 4,65 (m, 1H), 4,05 (s, 3H), 3,16-3,28 (m, 4H), 2,59 (s, 3H)

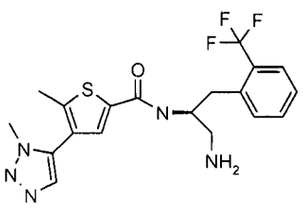
Ejemplo 310



Preparación de *N*-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(2-fluorofenil)propil]carbamato de 1,1-dimetiletilo. LC-MS (ES) m/z 360,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,60 (s, 1H), 8,43 (d, J = 1 Hz, 1H), 8,24 (d, J = 1 Hz, 1H), 7,37 (m, 1H), 7,27 (m, 1H), 7,08 (m, 2H), 4,66 (m, 1H), 4,19 (s, 3H), 3,27 (m, 2H), 3,10 (s, 2H)

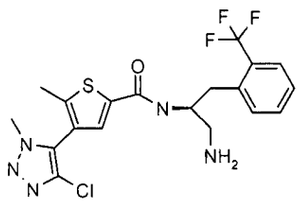
Ejemplo 311



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 260, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-5-metil-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 360,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,31 (s, 1H), 7,94 (s, 1H), 7,70 (m, 1H), 7,56 (m, 2H), 7,43 (m, 1H), 4,65 (m, 1H), 4,19 (s, 3H), 3,15-3,28 (m, 4H), 2,50 (s, 3H).

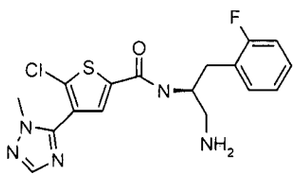
Ejemplo 312



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-5-metil-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 261, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-5-metil-2-tienil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil} carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 458,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 7,70 (m, 2H), 7,55 (m, 2H), 7,44 (m, 1H), 4,67 (m, 1H), 3,99 (s, 3H), 3,12-3,21 (m, 4H), 2,42 (s, 3H).

Ejemplo 313

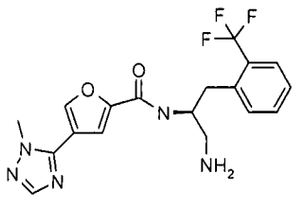


Preparación de *N*-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-fluorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 394,2 $(M+H)^+$, ^1H RMN (d_4-MeOH,

400 MHz) 8,49 (s, 1H), 7,95 (s, 1H), 7,27-7,36 (m, 2H), 7,06-7,13 (m, 2H), 4,61 (m, 1H), 4,03 (s, 3H), 3,02-3,25 (m, 4H).

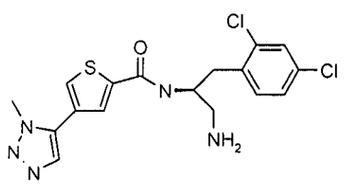
Ejemplo 314



Preparación de *N*-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-furanocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por {(2*S*)-2-{[(4-bromo-2-furanil)carbonil]amino}-3-[2-(trifluorometil)fenil]propil}carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 394,2 $(M+H)^+$, ^{1}H RMN (d_4-MeOH, 400 MHz) 8,50 (s, 1H), 8,43 (s, 1H), 7,71 (m, 1H), 7,61 (s, 1H), 7,54 (m, 2H), 7,42 (m, 1H), 4,66 (m, 1H), 4,14 (s, 3H), 3,25 (m, 2H), 3,14 (m, 2H).

Ejemplo 315

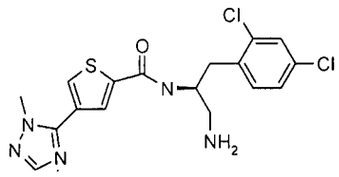


Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 260, con la excepción de que se sustituyó ((2S)-2-{[(4-

bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(2,4-diclorofenil)propil]carbamato (de la Preparación 22) de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 410,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,23 (s, 1H), 8,14 (m, 2H), 7,47 (d, J = 1 Hz, 1H), 7,41 (d, J = 1 Hz, 1H), 7,25 (m, 1H), 4,68 (m, 1H), 4,30 (s, 3H), 3,11-3,28 (m, 4H).

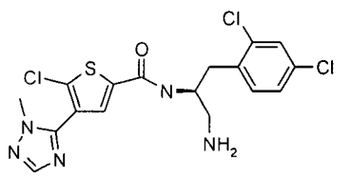
Ejemplo 316



Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(2,4-diclorofenil)propil]carbamato de 1,1-dimetiletilo (de la Preparación 22). El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 410,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,71 (s, 1H), 8,47 (d, J = 1 Hz, 1H), 8,34 (d, J = 1 Hz, 1H), 7,45 (m, 2H), 7,23 (m, 1H), 4,71 (m, 1H), 4,23 (s, 3H), 3,14-3,22 (m, 4H)

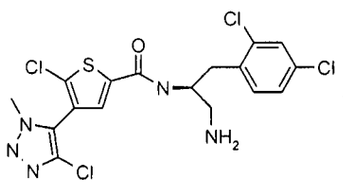
Ejemplo 317



Preparación de N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(2,4-diclorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 446,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,65 (s, 1H), 8,11 (s, 1H), 7,44 (m, 2H), 7,25 (m, 1H), 4,68 (m, 1H), 4,08 (s, 3H), 3,10-3,23 (m, 4H).

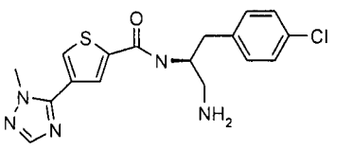
Ejemplo 318



Preparación de *N*-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 261, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(2,4-diclorofenil)propil]carbamato (de la Preparación 21) de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 480,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 7,80 (m, 1H), 7,48 (m, 1H), 7,39 (m, 1H), 7,27 (m, 1H), 4,66 (m, 1H), 4,05 (s, 3H), 3,08-3,14 (m, 4H)

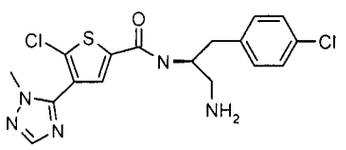
Ejemplo 319



Preparación de *N*-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 291, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-clorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 376,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,68 (s, 1H), 8,46 (d, J = 1 Hz, 1H), 8,29 (d, J = 1 Hz, 1H), 7,27-7,34 (m, 4H), 4,57 (m, 1H), 4,21 (s, 3H), 3,25 (m, 2H), 3,04 (m, 2H)

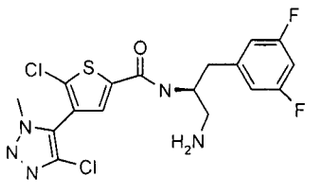
Ejemplo 320



Preparación de *N*-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 292, con la excepción de que se sustituyó [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,4-difluorofenil)propil]carbamato de 1,1-dimetiletilo por [(2*S*)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-clorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 410,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,47 (s, 1H), 7,97 (s, 1H), 7,30 (m, 4H), 4,60 (m, 1H), 4,03 (s, 3H), 3,22 (m, 2H), 3,00 (m, 2H).

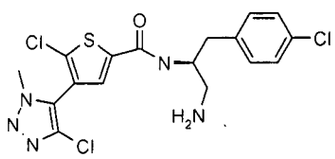
Ejemplo 321



Preparación de N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 261, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(3,5-difluorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 446,0 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 7,80 (s, 1H), 6,95 (m, 2H), 6,84 (m, 1H), 4,62 (m, 1H), 4,04 (s, 3H), 3,20 (m, 2H), 3,01 (m, 2H).

Ejemplo 322

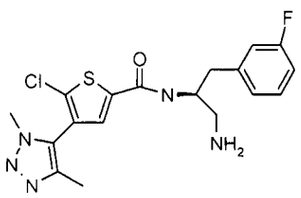


Preparación de *N*-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el Ejemplo 261, con la excepción de que se sustituyó ((2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-fenilpropil)carbamato de 1,1-dimetiletilo por [(2S)-2-{[(4-bromo-2-tienil)carbonil]amino}-3-(4-clorofenil)propil]carbamato de 1,1-dimetiletilo. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 444,0 $(M+H)^+$, ^1H RMN (d_4-

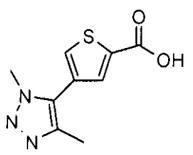
MeOH, 400 MHz) 7,73 (s, 1H), 7,30 (m, 4H), 4,66 (m, 1H), 4,04 (s, 3H), 3,18 (m, 2H), 2,99 (m, 2H).

Ejemplo 323



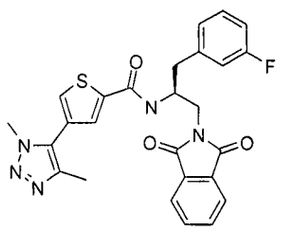
Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

a) ácido 4-(1,4-dimetil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico



Este intermedio se preparó de acuerdo con los procedimientos del Ejemplo 269 a) y b) con la excepción de que se sustituyó 1-metil-5-(tributilestannanil)-1*H*-1,2,3-triazol por 1,4-dimetil-5-(tributilestannanil)-1*H*-1,2,3-triazol (de la Preparación 21) y se sustituyó 4-bromo-5-cloro-2-tiofenocarboxilato de metilo por 4-bromo-2-tiofenocarboxilato de metilo. LC-MS (ES) m/z 224,2 $(M+H)^+$.

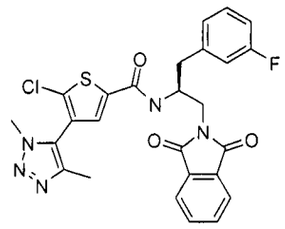
b) 4-(1,4-Dimetil-1H-1,2,3-triazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida



Este intermedio se preparó de acuerdo con el procedimiento del Ejemplo 269 c) con la excepción de que se sustituyó ácido 5-cloro-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico por ácido 4-(1,4-dimetil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxílico y se sustituyó 2-{(2*S*)-2-amino-3-[2-(trifluorometil)fenil]propil}-1*H*-

isoindolo-1,3(2*H*)-diona por 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona. LC-MS (ES) m/z 504,2 $(M+H)^+$.

c) 5-cloro-4-(1,4-dimetil-1*H*-1,2,3-triazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida

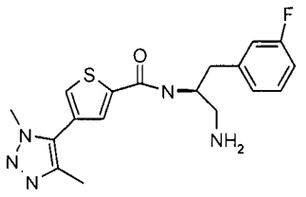


Una solución de 4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-N-{(1S)-2-(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida (254 mg, 0,454 mmol) y NCS (60,6 mg, 0,454 mmol) en N,N-dimetilformamida (DMF) (5 ml) se calentó a 40°C durante una noche. La mezcla de reacción se recogió en EtOAc, que se lavó 3 veces con H_2O y salmuera, se secó (Na_2SO_4) y se concentró. El residuo se purificó sobre una columna Biotage de 25 g, que se eluyó con EtOAc al 50-100%/hexano para dar 76 mg (28%) del producto en forma de un sólido espumoso de color blanco y 63 mg de material de partida recuperado. LC-MS (ES) m/z 538,0 $(M+H)^+$.

d) *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 269 d), con la excepción de que se sustituyó 5-cloro-*N*-((1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida por 5-cloro-4-(1,4-dimetil-1*H*-1,2,3-triazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida. El compuesto final se purificó por RP-HPLC y se convirtió en la sal HCl con una solución acuosa 2 N de HCl. LC-MS (ES) m/z 408,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 7,88 (m, 1H), 7,30 (m, 1H), 7,10 (m, 2H), 6,96 (m, 1H), 4,65 (m, 1H), 4,10 (s, 3H), 3,21 (m, 2H), 3,03 (m, 2H), 2,06 (s, 3H).

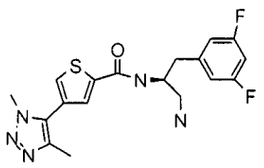
Ejemplo 324



Preparación de *N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con los procedimientos del Ejemplo 323 a), b) y d), con la excepción de que se sustituyó 5-cloro-4-(1,4-dimetil-1*H*-1,2,3-triazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida por 4-(1,4-dimetil-1*H*-1,2,3-triazol-5-il)-*N*-{(1*S*)-2-(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)-1-[(3-fluorofenil)metil]etil}-2-tiofenocarboxamida. LC-MS (ES) m/z 374,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,09 (d, J = 1 Hz, 1H), 8,06 (d, J = 1 Hz, 1H), 7,31 (m, 1H), 7,16 (m, 1H), 6,96 (m, 1H), 4,56 (m, 1H), 4,20 (s, 3H), 3,23 (m, 2H), 3,05 (m, 2H), 2,47 (s, 3H).

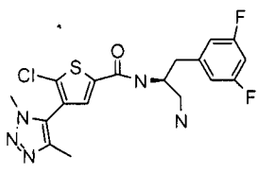
Ejemplo 325



Preparación de *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con los procedimientos del Ejemplo 323 a), b) y d), con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona. LC-MS (ES) m/z 392,2 $(M+H)^+$, ^1H RMN (d_4-MeOH, 400 MHz) 8,13 (m, 2H), 6,99 (m, 2H), 6,79 (m, 1H), 4,59 (m, 1H), 4,22 (s, 3H), 3,26 (m, 2H), 3,06 (m, 2H), 2,49 (s, 3H).

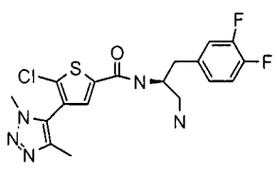
Ejemplo 326



Preparación de *N*-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 323, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2*S*)-2-amino-3-(3,5-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona. LC-MS (ES) m/z 426,2 $(M+H)^+$, ^{1}H RMN (d_4-MeOH, 400 MHz) 7,88 (s, 1H), 6,96 (m, 2H), 6,82 (m, 1H), 4,62 (m, 1H), 4,07 (s, 3H), 3,22 (m, 2H), 3,05 (m, 2H), 2,34 (s, 3H).

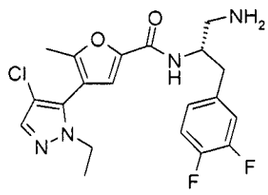
Ejemplo 327



Preparación de *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida

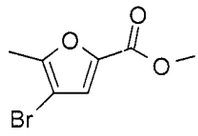
El compuesto del título se preparó en forma de un sólido de color blanco de acuerdo con el procedimiento del Ejemplo 323, con la excepción de que se sustituyó 2-[(2*S*)-2-amino-3-(3-fluorofenil)propil]-1H-isoindolo-1,3(2H)-diona por 2-[(2*S*)-2-amino-3-(3,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona. LC-MS (ES) m/z 426,2 $(M+H)^+$, ^{1}H RMN (d_4-MeOH, 400 MHz) 7,87 (s, 1H), 7,12-7,26 (m, 3H), 4,62 (m, 1H), 4,08 (s, 3H), 3,21 (m, 2H), 3,00 (m, 2H), 2,36 (s, 3H).

Ejemplo 328



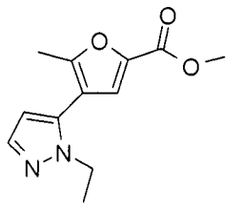
N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida

a) 4-bromo-5-metil-2-furanocarboxilato de metilo



A una solución de 4,5-dibromo-2-furanocarboxilato de metilo (4,5 g, 15,85 mmol) y CLORURO DE BIS(TRIFENILFOSFINA)PALADIO (II) (0,38 g, 0,541 mmol) en THF (100 ml) a TA se le añadió gota a gota cloro(metil)cinc (15 ml, 30 mmol). Después de agitar durante 10 h, la reacción se interrumpió con NH_4Cl (sat.) (50 ml). La mezcla se extrajo con EtOAc (50 ml x 3) y las capas orgánicas recogidas se secaron sobre $MgSO_4$. El disolvente se retiró al vacío y el residuo resultante se purificó por cromatografía en columna (sílice, EtOAc/Hex al 10-20%) para dar el compuesto del título (2,5 g, 72%) en forma de un sólido de color blanco: LC-MS (ES) m/z 220 $(M+H)^+$.

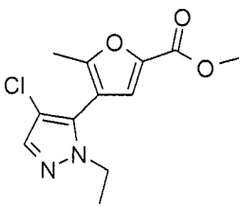
b) 4-(1-etil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo



A un matraz cerrado herméticamente de 100 ml se le añadieron 1-etil-5-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2-il)-1H-pirazol (2,2 g, 9,91 mmol), carbonato potásico (2,84 g, 20,54 mmol), 4-bromo-5-metil-2-furanocarboxilato de metilo (1,5 g, 6,85 mmol) y BIS(TRI-T-BUTILFOSFINA)PALADIO (0) (0,175 g, 0,34 mmol) en 1,2-dimetoxietano (6 ml) y H_2O (1 ml). Después de agitar durante 2 h a 72ºC, la

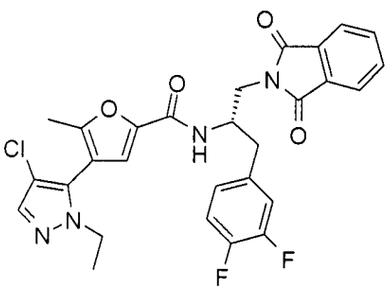
solución de reacción se diluyó con DCM (50 ml) y se lavó con H_2O. La capa orgánica se secó Na_2SO_4, se filtró y se concentró. El residuo se purificó sobre gel de sílice [EtOAc/hexanos, al 10-30%] para dar el producto [1,1 g, 68,6%] en forma de un sólido de color blanquecino: LC-MS (ES) m/z 235 $(M+H)^+$.

c) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo



Una mezcla de 4-(1-etil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo (950 mg, 4,06 mmol) y NCS (650 mg, 4,87 mmol) en THF (10 ml) se calentó a 70°C en un tubo cerrado herméticamente. Después de 2 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 10-20%/Hexano), produciendo el compuesto del título (970 mg, 89%) en forma de un sólido de color blanco: LC-MS (ES) m/z 269 $(M+H)^+$.

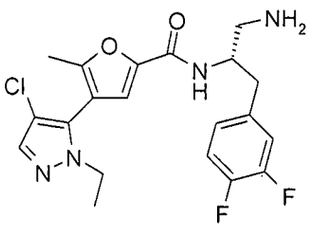
d) 4-(4-cloro-1-etil-1*H*-pirazol-5-il)-*N*-{(1*S*)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2*H*-isoindol-2-il)metil]etil}-5-metil-2-furanocarboxamida



A una solución de 4-(4-cloro-1-etil-1H-pirazol-5-il)-5-metil-2-furanocarboxilato de metilo (500 mg, 1,86 mmol) en THF/H_2O (5 ml/1 ml) se le añadió KOH (500 mg, 8,91 mmol). La mezcla de reacción se calentó a 58°C durante 4 h. La mezcla se concentró, se diluyó con H_2O (2 ml) y el valor del pH se ajustó a 3. La mezcla se extrajo con DCM (10 ml x 3). Las capas orgánicas recogidas se concentraron al vacío para dar un ácido bruto (460 mg, 97%), que se usó directamente sin purificación adicional: LC-MS (ES) m/z 255 $(M+H)^+$.

Al ácido anterior (221 mg, 0,869 mmol) en DCM (5 ml) a 25ºC se le añadió en una porción PyBrOP (480 mg, 1,03 mmol), seguido de la adición de DIPEA (1,0 ml, 5,73 mmol). Después de 10 min, a la solución de reacción se le añadió 2-[(2S)-2-amino-3-(3,4-difluorofenil)propil]-1H-isoindolo-1,3(2H)-diona (250 mg, 0,79 mmol). Después de 1 h, la mezcla de reacción se concentró y se purificó por cromatografía en columna (sílice, EtOAc al 30-50%/Hexano), produciendo el compuesto del título (401 mg, 92%) en forma de un sólido de color blanco: LC-MS (ES) m/z 553 $(M+H)^+$.

e) *N*-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida



A ta, se añadió NH_2NH_2 (0,5 ml, 15,93 mmol) a 4-(4-cloro-1-etil-1H-pirazol-5-il)-N-{(1S)-2-(3,4-difluorofenil)-1-[(1,3-dioxo-1,3-dihidro-2H-isoindol-2-il)metil]etil}-5-metil-2-furanocarboxamida (260 mg, 0,47 mmol) en MeOH (5 ml). Después de 48 h, el disolvente se retiró al vacío. El residuo resultante se recogió en DCM (20 ml), y se lavó con H_2O (20 ml x 3).

A la solución en DCM se le añadió HCl (al 36%, 10 ml, 120 mmol). Después de 1 h, la fase acuosa se separó y se lavó con DCM (30 ml x 3). El agua se retiró a alto vacío para dar el compuesto del título (140 mg, 69,7%) en forma de un sólido de color blanquecino: LC-MS (ES) m/z 423 $(M+H)^+$, RMN (d_4-MeOD, 400 MHz) ppm 7,59 (s, 1H), 7,27-7,16 (m, 3H), 7,13-7,08 (m, 1H), 4,56 (m, 1H), 4,06 (c, J = 7,3 Hz, 2H), 3,26-3,22 (m, 1H), 3,17-3,11 (m, 1H), 3,05-3,00 (m, 1H), 2,97-2,91 (m, 1H), 2,36 (s, 3H) y 1,33 (t, J = 7,3 Hz, 3H).

Ejemplo 329 - Composición de la Cápsula

Se produce una forma de dosificación oral para administrar la presente invención rellenando una cápsula de gelatina dura de dos piezas convencional con los ingredientes en las proporciones mostradas en la Tabla I, presentada a continuación.

Tabla I

INGREDIENTES	CANTIDADES
N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida (Compuesto del Ejemplo 1)	25 mg
Lactosa	55 mg
Talco	16 mg
Estearato de magnesio	4 mg

Ejemplo 330 - Composición Parenteral Inyectable

Una forma inyectable para administrar la presente invención se produce agitando 1,5% en peso de *N*-(2-amino-1-feniletil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida (Compuesto del Ejemplo 2) en 10% en volumen de propilenglicol en agua.

Ejemplo 331 - Composición de Comprimidos

La sacarosa, el sulfato cálcico dihidrato, y un inhibidor de Akt como se muestra a continuación en la Tabla II, se mezclan y se granulan en las proporciones mostradas con una solución de gelatina al 10%. Los gránulos húmedos se tamizan, se secan, se mezclan con el almidón, el talco y el ácido esteárico, se tamizan y se comprimen en un comprimido.

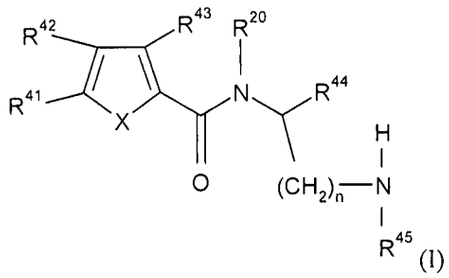
Tabla II

INGREDIENTES	CANTIDADES
N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida (Compuesto del Ejemplo 3)	20 mg
sulfato cálcico dihidrato	30 mg
sacarosa	4 mg
almidón	2 mg
talco	1 mg
ácido esteárico	0,5 mg

Aunque las realizaciones preferidas de la invención se ilustran por lo anterior, debe entenderse que la invención no se limita a las instrucciones precisas descritas en este documento y que está reservado el derecho a que todas las modificaciones entren dentro del alcance de las siguiente reivindicaciones.

REIVINDICACIONES

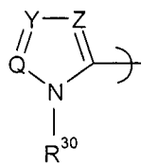
1. Un compuesto de Fórmula (I):



(I)

en la que:

R^{41} y R^{42} se seleccionan independientemente entre: hidrógeno,



, halógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, alquiloxi C_{1-4}, alquiloxi C_{1-4} sustituido, furano, furano sustituido, tiofeno y tiofeno sustituido,

donde Q y Y se seleccionan independientemente entre: nitrógeno y $-C(R^{70})-$, y Z se selecciona entre: nitrógeno y $-C(R^{48})-$, con la condición de que al menos uno y como mucho 2 de Q, Y y Z sean nitrógeno, y R^{30} se selecciona entre: alquilo C_{1-4} y alquilo C_{1-4} sustituido con uno a tres átomos de flúor,

donde R^{70} se selecciona entre: hidrógeno, y halógeno, y

R^{48} se selecciona entre: hidrógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, arilo, arilo sustituido, heteroarilo, heteroarilo sustituido, cicloalquilo, cicloalquilo sustituido, heterocicloalquilo, heterocicloalquilo sustituido y halógeno;

R^{43} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4}, alquilo C_{1-4} sustituido, alquiloxi C_{1-4}, alquiloxi C_{1-4} sustituido, furano y tiofeno;

R^{44} está ausente o se selecciona entre: $-(CR^{60}R^{61})_mAR$ donde el grupo AR está sin sustituir, $-(CR^{60}R^{61})_mAR$ donde el grupo AR está sustituido y alquilo C_{1-6},

donde m es de 0 a 3 y AR es un anillo, aromático o no aromático, saturado o insaturado, cíclico o policíclico, que contiene de 3 a 16 átomos de carbono y que contiene opcionalmente de uno a tres heteroátomos, con la condición de que cuando el anillo es aromático y el número de átomos de carbono es 3, el anillo contenga al menos dos heteroátomos y cuando el anillo es aromático y el número de átomos de carbono es 4, el anillo contenga al menos un heteroátomo, y

R^{60} y R^{61} se seleccionan independientemente entre: hidrógeno y alquilo C_{1-4}, con la condición de que cuando m es 3, no más de 4 de R^{60} y R^{61}, cuando se añaden juntos, sean alquilo C_{1-4},

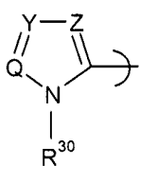
R^{45} se selecciona entre hidrógeno y alquilo C_{1-4};

R^{20} se selecciona entre hidrógeno, alquilo C_{1-4} e hidroxi;

X se selecciona entre O, S y NR^{49},

donde R^{49} se selecciona entre hidrógeno y alquilo C_{1-4}; y

n es de 0 a 2 y este resto está opcionalmente, si es aplicable, sustituido con hidroxialquilo C_{1-4};

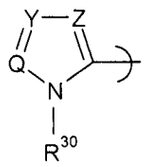
con la condición de que uno y sólo uno de R^{41} y R^{42} sea 

;

y/o una sal farmacéuticamente aceptable del mismo.

2. Un compuesto de Fórmula (I), como se ha definido en la reivindicación 1, en la que:

R^{41} y R^{42} se seleccionan independientemente entre: hidrógeno,



, halógeno, alquilo C_{1-4}, trifluorometilo, metoxi y furano,

donde Q es nitrógeno, Y se selecciona entre: nitrógeno y $-C(R^{70})-$, y Z se selecciona entre: nitrógeno y $-C(R^{48})-$, con la condición de que como máximo uno de Y y Z sea nitrógeno, y R^{30} sea alquilo C_{1-4},

donde R^{70} se selecciona entre: hidrógeno, y halógeno, y

R^{48} se selecciona entre: hidrógeno, alquilo C_{1-4}, trifluorometilo, fenilo, ciclopropilo y halógeno;

R^{43} se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4} y metoxi;

R^{44} está ausente o se selecciona entre: $-(CR^{60}R^{61})_mAAR$ donde el grupo AAR está sin sustituir, $-(CR^{60}R^{61})_mAAR$ donde el grupo AAR está sustituido y alquilo C_{1-6},

donde m es de 0 a 3 y AAR se selecciona entre fenilo, indol, naftaleno, piridina y ciclohexilo, y

R^{60} y R^{61} se seleccionan independientemente entre: hidrógeno y metilo, con la condición de que cuando m es 3 no más de 4 de R^{60} y R^{61}, cuando se añaden juntos, sean metilo,

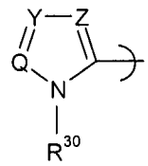
R^{45} se selecciona entre hidrógeno y alquilo C_{1-4};

R^{20} se selecciona entre hidrógeno, metilo e hidroxi;

X se selecciona entre O, S y NR^{49},

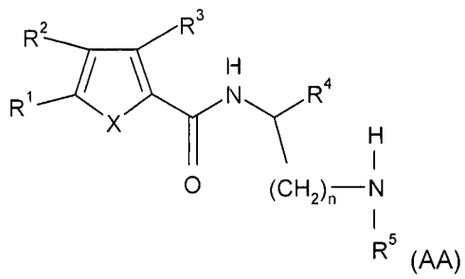
donde R^{49} se selecciona entre hidrógeno y metilo; y

n es de 1 a 2 y este resto está opcionalmente sustituido con hidroxilmetilo;

con la condición de que uno y sólo uno de R^{41} y R^{42} sea  ;

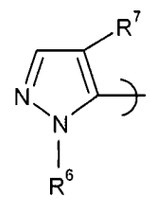
y/o sales farmacéuticamente aceptables de los mismos.

3. Un compuesto de la reivindicación 1 representado por la siguiente Fórmula (AA):



(AA)

en la que:



R^1 y R^2 se seleccionan independientemente entre: hidrógeno, halógeno, alquilo C_{1-4}, furano y tiofeno,
donde R^6 es alquilo C_{1-4} y R^7 se selecciona entre hidrógeno, alquilo C_{1-4} y halógeno;

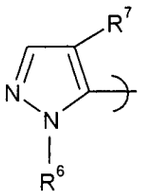
R^3 se selecciona entre: hidrógeno, halógeno, alquilo C_{1-4}, furano y tiofeno;

R^4 se selecciona entre $-(CH_2)_m$arilo y $-(CH_2)_m$arilo donde el arilo está sustituido,
donde m es de 0 a 2;

R^5 se selecciona entre hidrógeno y alquilo C_{1-4};

X se selecciona entre O y S; y

n es de 0 a 2;

con la condición de que uno y sólo uno de R^1 y R^2 sea  y con la condición adicional de que al menos uno de R^1, R^2 y R^3 sea hidrógeno;

y/o una sal farmacéuticamente aceptable del mismo.

4. Un compuesto de la reivindicación 1 seleccionado entre:

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-(2-amino-1-feniletil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida;

N-(2-amino-1-feniletil)-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida;

N-(2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-(2-amino-1-feniletil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(3-furanil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-3-(metiloxi)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[3-amino-1-(fenilmetil)propil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

4-bromo-N-[2-(metilamino)-1-feniletil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-4-fenil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-cloro-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(4-bromo-1-metil-1H-pirazol-5-il)-4-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-fluoro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[1-(aminometil)-3-fenilpropil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[1-(aminometil)-3-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

4-bromo-*N*-[3-(metilamino)-1-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[3-(metilamino)-1-fenilpropil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

4-bromo-*N*-[2-(metilamino)-1-(fenilmetil)etil]-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida

N-((1*S*)-2-amino-1-{[4-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[1-(aminometil)-2-metil-2-fenilpropil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida;

N-[2-amino-1-(fenilmetil)etil]-1-metil-5-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida;

N-[2-amino-1-(fenilmetil)etil]-1-metil-4-(1-metil-1*H*-pirazol-5-il)-1*H*-pirrol-2-carboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-(metilamino)-1-(fenilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-*N*-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[1-(aminometil)-2-metil-2-fenilpropil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[4-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1*H*-imidazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-clorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(1*H*-indol-3-ilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-clorofenil)metil]etil}-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2-fluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(1-naftalenil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(1-naftalenil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{2-amino-1-[2-(trifluorometil)fenil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{2-amino-1-[2-(trifluorometil)fenil]etil}-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-clorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-clorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-(3-amino-1-fenilpropil)-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-3,4-dibromo-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-*N*-hidroxi-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-3-(metiloxi)-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-fluoro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-metil-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1H-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-[1-metil-4-(1-metiletil)-1H-pirazol-5-il]-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-propil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-etil-4-(1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1-metil-4-propil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-4-etil-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-diclorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,6-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,4-difluorofenil)metil]etil}-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-ciclopropil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(3-cloro-1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-etil-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(metiloxi)-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(2,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-cloro-5-(4-bromo-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(3-piridinilmetil)etil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*R*)-2-amino-1-feniletil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(3-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(2-clorofenil)etil]-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-fluorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-[2-amino-1-(2-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(3-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-(2-aminoetil)-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(4-clorofenil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-(ciclohexilmetil)etil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-feniletil]-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-[(1*S*)-2-amino-1-metiletil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[3-(trifluorometil)fenil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-[(1*S*)-1-(aminometil)-3-metilbutil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-metil-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1,4-dimetil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-pirazol-5-il)-5-(trifluorometil)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

(*N*-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1,4-dietil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-etil-4-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-3-metil-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-[1-metil-4-(trifluorometil)-1*H*-pirazol-5-il]-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-propil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(4-bromo-1-metil-1H-1,2,3-triazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(fenilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1*S*)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1*H*-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1S)-2-amino-1-(ciclohexilmetil)etil]-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2-fluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-metil-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(1-metil-1H-1,2,4-triazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(2,4-diclorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-clorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,5-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-1,2,3-triazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(1-metil-1H-1,2,4-triazol-5-il)-2-tiofenocarboxamida;

N-[(1*S*,2*S*)-2-amino-3-hidroxi-1-fenilpropil]-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-1,2,3-triazol-5-il)-2-furanocarboxamida; y

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-5-metil-2-furanocarboxamida;

y/o una sal farmacéuticamente aceptable del mismo.

5. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 1, y/o una sal farmacéuticamente aceptable del mismo y un vehículo farmacéuticamente aceptable.

6. Un proceso para preparar una composición farmacéutica que contiene un vehículo o diluyente farmacéuticamente aceptable y una cantidad eficaz de un compuesto de Fórmula (I) como se ha descrito en la reivindicación 1 y/o una sal farmacéuticamente aceptable del mismo, comprendiendo el proceso asociar el compuesto de Fórmula (I) y/o una sal farmacéuticamente aceptable del mismo con un vehículo o diluyente farmacéuticamente aceptable.

7. Un método para tratar o disminuir la gravedad de una enfermedad o afección seleccionada entre cáncer y artritis en un mamífero que lo necesita, que comprende administrar a dicho mamífero una cantidad terapéuticamente eficaz de un compuesto de Fórmula I, como se ha descrito en la reivindicación 1 y/o una sal farmacéuticamente aceptable del mismo.

8. El método de la reivindicación 7, en el que el mamífero es un ser humano.

9. Un método para tratar o disminuir la gravedad de una enfermedad o afección seleccionada entre cáncer y artritis en un mamífero que lo necesita, que comprende administrar a dicho mamífero una cantidad terapéuticamente eficaz de un compuesto de Fórmula (AA), como se ha descrito en la reivindicación 3 y/o una sal farmacéuticamente aceptable del mismo.

10. El método de la reivindicación 9, en el que el mamífero es un ser humano.

11. El método de acuerdo con la reivindicación 7, en el que dicho cáncer se selecciona entre: cerebral (gliomas), glioblastomas, síndrome de Bannayan-Zonana, enfermedad de Cowden, enfermedad de Lhermitte-Duclos, de mama, de colon, de cabeza y cuello, de riñón, de pulmón, de hígado, melanoma, de ovario, pancreático, de próstata, sarcoma y tiroideo.

12. El método de acuerdo con la reivindicación 9, en el que: dicho cáncer se selecciona entre cerebral (gliomas), glioblastomas, síndrome de Bannayan-Zonana, enfermedad de Cowden, enfermedad de Lhermitte-Duclos, de mama, de colon, de cabeza y cuello, de riñón, de pulmón, de hígado, melanoma, de ovario, pancreático, de próstata, sarcoma y tiroideo.

13. Uso de un compuesto de Fórmula (I), como se ha descrito en la reivindicación 1 y/o una sal farmacéuticamente aceptable del mismo, en la preparación de un medicamento para uso en el tratamiento o disminución de la gravedad de una enfermedad o afección seleccionada entre cáncer y artritis.

14. El método de inhibición de la actividad de Akt en un mamífero que lo necesita, que comprende administrar a dicho mamífero una cantidad terapéuticamente eficaz de un compuesto de Fórmula I, como se ha descrito en la reivindicación 1 y/o una sal farmacéuticamente aceptable del mismo.

15. El método de la reivindicación 14, en el que el mamífero es un ser humano.

16. Un método de tratamiento de cáncer en un mamífero que lo necesita, que comprende: administrar a dicho mamífero una cantidad terapéuticamente eficaz de

a) un compuesto de Fórmula (I), como se ha descrito en la reivindicación 1 y/o una sal farmacéuticamente aceptable del mismo; y

b) al menos un agente antineoplásico.

17. El método de la reivindicación 16, donde al menos un agente antineoplásico se selecciona entre el grupo que consiste esencialmente en agentes anti-microtubulares, complejos de coordinación de platino, agentes alquilantes, agentes antibióticos, inhibidores de topoisomerasa II, antimetabolitos, inhibidores de topoisomerasa I, hormonas y análogos hormonales, inhibidores de la ruta de transducción de señales; inhibidores de la angiogénesis de tirosina quinasa no asociada a receptores; agentes inmunoterapéuticos; agentes proapoptóticos; e inhibidores de la señalización del ciclo celular.

18. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es un agente anti-microtubular seleccionado entre diterpenoides y alcaloides de la vinca.

19. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es un diterpenoide.

20. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es un alcaloide de la vinca.

21. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es un complejo de coordinación de platino.

22. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es paclitaxel, carboplatino o vinorelbina.

23. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es paclitaxel.

24. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es carboplatino.

25. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es vinorelbina.

26. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es un inhibidor de la ruta de transducción de señales.

27. El método de la reivindicación 26, donde el inhibidor de la ruta de transducción de señales es un inhibidor de una quinasa asociada al receptor de un factor de crecimiento seleccionado entre el grupo que consiste en VEGFR2, TIE2, PDGFR, BTK, IGFR-1, TrkA, TrkB, TrkC y c-fms.

28. El método de la reivindicación 26, donde el inhibidor de la ruta de transducción de señales es un inhibidor de una serina/treonina quinasa seleccionada entre el grupo que consiste en rafk, akt y PKC-zeta.

29. El método de la reivindicación 26, donde el inhibidor de la ruta de transducción de señales es un inhibidor de una serina/treonina quinasa seleccionada entre la familia de quinasas src.

30. El método de la reivindicación 29, donde el inhibidor de la ruta de transducción de señales es un inhibidor de c-src.

31. El método de la reivindicación 26, donde el inhibidor de la ruta de transducción de señales es un inhibidor del oncogén Ras seleccionado entre inhibidores de farnesil transferasa y geranilgeranil transferasa.

32. El método de la reivindicación 26, donde el inhibidor de la ruta de transducción de señales es un inhibidor de una serina/treonina quinasa seleccionada entre el grupo que consiste en PI3K.

33. El método de la reivindicación 16, donde dicho al menos un agente antineoplásico es un inhibidor de la señalización del ciclo celular.

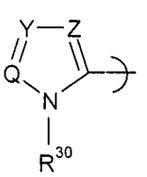
34. El método de la reivindicación 33, donde el inhibidor de la señalización del ciclo celular se selecciona entre inhibidores del grupo CDK2, CDK4 y CDK6.

35. Una combinación farmacéutica de acuerdo con la reivindicación 16 para uso en terapia.

36. El uso de una combinación farmacéutica de acuerdo con la reivindicación 16 para la preparación de un medicamento útil en el tratamiento de cáncer.

37. Un compuesto de Fórmula (I), como se ha definido en la reivindicación 1, en la que:

R^{41} se selecciona entre: cloro, etilo, metilo y metoxi;

R^{42} es 

,

donde Q es nitrógeno, Y es –CH- y Z es $-C(R^{48})-$, y

R^{30} se selecciona entre metilo y etilo,

donde R^{48} se selecciona entre: hidrógeno, metilo, cloro y bromo;

R^{43} es hidrógeno;

R^{44} es $-CH_2$-fenilo donde el grupo fenilo está sustituido con uno o dos sustituyentes seleccionados entre flúor y trifluorometilo;

R^{45} es hidrógeno;

R^{20} es hidrógeno;

X se selecciona entre O y S; y

n es 1;

y/o una sal farmacéuticamente aceptable del mismo.

38. El método de acuerdo con la reivindicación 7, en el que dicho cáncer se selecciona entre: cerebral (gliomas), glioblastomas, síndrome de Bannayan-Zonana, enfermedad de Cowden, enfermedad de Lhermitte-Duclos, de mama, cáncer de mama inflamatorio, tumor de Wilm, sarcoma de Ewing, Rabdomiosarcoma, ependimoma, meduloblastoma, de colon, de cabeza y cuello, de riñón, de pulmón, de hígado, melanoma, de ovario, pancreático, de próstata, sarcoma, osteosarcoma, tumor óseo de células gigantes, tiroideo, leucemia linfoblástica de células T, leucemia mielógena crónica, leucemia linfocítica crónica, leucemia de células pilosas, leucemia linfoblástica aguda, leucemia mielógena aguda, leucemia neutrofílica crónica, leucemia de células T linfoblástica aguda, plasmacitoma, leucemia inmunoblástica de células grandes, leucemia de células del manto, mieloma múltiple, leucemia megacarioblástica, mieloma múltiple, leucemia megacariocítica aguda, leucemia promielocítica, eritroleucemia, linfoma maligno, linfoma de hodgkin, linfoma no Hodgkin, linfoma linfoblástico de células T, linfoma de Burkitt, linfoma folicular, neuroblastoma, cáncer de vejiga, cáncer urotelial, cáncer de pulmón, cáncer vulvar, cáncer cervical, cáncer endometrial, cáncer renal, mesotelioma, cáncer esofágico, cáncer de las glándulas salivales, cáncer hepatocelular, cáncer gástrico, cáncer nasofaríngeo, cáncer oral, cáncer de la boca, GIST (tumor estromático gastrointestinal) y cáncer testicular.

39. El método de la reivindicación 38, en el que el mamífero es un ser humano.

40. Un compuesto de la reivindicación 3 seleccionado entre:

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-(2-amino-1-feniletil)-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida;

N-(2-amino-1-feniletil)-4-{[(2Z)-1-metil-2-(2-propen-1-ilideno)hidrazino]metil}-2-tiofenocarboxamida;

N-(2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-[2-amino-1-(fenilmetil)etil]-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-(2-amino-1-feniletil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-bromo-5-(1-metil-1H-pirazol-5-il)-2-furanocarboxamida; y

N-[2-amino-1-(fenilmetil)etil]-4-metil-5-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

y/o una sal farmacéuticamente aceptable del mismo.

41. Un compuesto de la reivindicación 1 seleccionado entre:

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1H-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1H-pirazol-5-il)-5-etil-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[2-(trifluorometil)fenil]metil}etil)-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1H-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-metil-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-((1S)-2-amino-1-{[3-(trifluorometil)fenil]metil}etil)-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(4-fluorofenil)metil]etil}-4-(4-bromo-1-metil-1*H*-pirazol-5-il)-5-cloro-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-5-(metiloxi)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1S)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

N-{(1*S*)-2-amino-1-[(4-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(1,4-dimetil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-tiofenocarboxamida; y

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-etil-1*H*-pirazol-5-il)-2-furanocarboxamida;

y/o una sal farmacéuticamente aceptable del mismo.

42. Un compuesto de la reivindicación 1 seleccionado entre:

N-{(1*S*)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-tiofenocarboxamida;

N-{(1S)-2-amino-1-[(3-fluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1H-pirazol-5-il)-2-furanocarboxamida; y

N-{(1*S*)-2-amino-1-[(3,4-difluorofenil)metil]etil}-5-cloro-4-(4-cloro-1-metil-1*H*-pirazol-5-il)-2-furanocarboxamida;

y/o una sal farmacéuticamente aceptable del mismo.

RESUMEN DE LA DESCRIPCIÓN

Se inventan nuevos compuestos heterocíclicos de carboxamida, el uso de tales compuestos como inhibidores de la actividad de la proteína quinasa B y en el tratamiento de cáncer y artritis.

1087

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:
WAYNE J. DUSTMAN
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY,
UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference PU62316	Date of mailing *(day/month/year)* 07 JUL 2008
International application No. PCT/US 08/53269	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
Applicant SMITHKLINE BEECHAM CORPORATION	International filing date *(day/month/year)* 07 February 2008 (07.02.2008)

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

   Filing of amendments and statement under Article 19:
   The applicant is entitled, if he so wishes, to amend the claims of the international application (see Rule 46):

   When? The time limit for filing such amendments is normally two months from the date of transmittal of the international search report.

   Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes 1211 Geneva 20, Switzerland, Facsimile No.: +41 22 740 14 35

   For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

   ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

   ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Reminders**

   Shortly after the expiration of **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

   The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

   Within **19 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

   In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 19 months.

   See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/220 (January 2004)

(See notes on accompanying sheet)

1088

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PU62316	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/US 08/53269	International filing date *(day/month/year)* 07 February 2008 (07.02.2008)	(Earliest) Priority Date *(day/month/year)* 07 February 2007 (07.02.2007)
Applicant SMITHKLINE BEECHAM CORPORATION		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 2 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

b. ☐ This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

c. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. ☐ **Certain claims were found unsearchable** (see Box No. II).

3. ☐ **Unity of invention is lacking** (see Box No. III).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

a. the figure of the **drawings** to be published with the abstract is Figure No. _____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

1089

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 08/53269

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/12 (2008.04)
USPC - 514/675
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
USPC - 514/675

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST(PGPB,USPT,USOC,EPAB,JPAB): thiophene, compounds, carboxamide, cancer, protein kinase B, CDK, PI3K, composition, carrier, mammal, human, breast, colon, kidney, lung, liver, combination, vinca alkaloid, vinorelbine, carboplatin, paclitaxel, signal transduction

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0712397 B1 (DUCKWORTH et al.) 21 Apr 1999 (21.04.1999); para [0003]-[0007]; para [0014]; para [0016]; para [0032] - para [0038].	1-42
Y	LIN et al. Discovery of 2-pyrimidyl-5-amidothiophenes as potent inhibitors for AKT: Synthesis and SAR studies. Bioorganic and Medicinal Chemistry Letters 15 Aug 2006, 16(16):4163-4168; pg 4163; pg 4166 - pg 4167	1-42
Y	WO 2006/136837 A2 (THOMPSON et al.) 28 Dec 2006 (28.12.2006); pg 1, ln 5-10; pg 5, ln 15 - pg 6, ln 30; pg 9, ln 7-10, 15-23; pg 11, ln 5-9; pg 14, ln 10-13; pg 16, ln 5-37; pg 18, ln 34-37; pg 76, ln 31 - pg 77, ln 36; pg 83, ln 39 - pg 86, ln 14; pg 88, ln 21- pg 89, ln 42; pg 95, ln 8 - pg 99, ln 35; pg 103, ln 11 - pg 105, ln 9; pg 118, ln 15 - pg 119, ln 36	7-36 and 38-39

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2008 (25.05.2008)	07 JUL 2008
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (April 2007)

10/990

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
WAYNE J. DUSTMAN
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY,
UW2220
709 SWEDELAND ROAD, P.O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	07 JUL 2008
Applicant's or agent's file reference PU62316	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 08/53269	07 February 2008 (07.02.2008)	07 February 2007 (07.02.2007)

International Patent Classification (IPC) or both national classification and IPC
IPC(8) - A61K 31/12 (2008.04)
USPC - 514/675

Applicant SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/US	Date of completion of this opinion	Authorized officer:
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	27 May 2008 (27.05.2008)	Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

1091

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/53269

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of:

   a. type of material

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material

      ☐ on paper

      ☐ in electronic form

   c. time of filing/furnishing

      ☐ contained in the international application as filed

      ☐ filed together with the international application in electronic form

      ☐ furnished subsequently to this Authority for the purposes of search

4. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

1092

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/53269

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-42	YES
	Claims	NONE	NO
Inventive step (IS)	Claims	NONE	YES
	Claims	1-42	NO
Industrial applicability (IA)	Claims	1-42	YES
	Claims	NONE	NO

2. Citations and explanations:

Claims 1-6, 37 and 40-42 lack an inventive step under PCT Article 33(3) as being obvious over EP 0712397 B1 to Duckworth et al. (hereinafter "Duckworth) in view of the article entitled "Discovery of 2-pyrimidyl-5-amidothiophenes as potent inhibitors for AKT: Synthesis and SAR studies" by Lin et al. (hereinafter "Lin").

Regarding claim 1, Duckworth discloses a compound of the formula:
(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-CO2H (para [0016]),

where R41 is a pyrazole such that Q is nitrogen, Y is -CR70, Z is -CR48, R30 is C1-6 alkyl, R70 is hydrogen or halogen and R48 is hydrogen or C1-6 alkyl (para [0003] - para [0007]); R42 is hydrogen or C1-6 alkyl, R43 is hydrogen or C1-6 alkyl, and X is O or S (para [0003] - para [0007]). The carboxylic acid is reacted, via the corresponding acid chloride, with an amine to form the resultant amide:

(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-CO2H + H2N-[substituted phenyl] -->
(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-C(O)-NH-[substituted phenyl] (para [0014])

Duckworth does not expressly disclose an amide of the formula:
(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-C(O)-N(R20)-CH(R44)((CH2)n-NH(R45). Lin discloses 2-pyrimidyl-5-amidothiophenes as potent AKT inhibitors (pg 4167). Specifically, Duckworth discloses compound 2aa as one of the most potent AKT inhibitors: pyrimidyl-(R42)(R43)-[5-membered X heterocycle]-C(O)-N(R20)-CH(R44)-(CH2)n-NH(R45),
where R42 and R43 are both hydrogen and X is S; R44 is -(CR60R61)m-AR where R60 and R61 are hydrogen, m is 1 and AR is a substituted phenyl with two chloro groups [R44 is -CH2-phenyl(Cl)2]; R20 is H; n is 1 and R45 is H (pg 4166).

It would have been obvious to one of ordinary skill in the art to add the teachings of Lin concerning a potent AKT inhibitor possessing the pharmacophore, -(R42)(R43)-[5-membered X heterocycle]-C(O)-N(R20)-CH(R44)-CH2-NH(R45), to the teachings of Duckworth concerning the carboxylic acid, (R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-CO2H, reacted with an amine

(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-CO2H + HN(R20)-CH(R44)-(CH2)n-NH(R45) --->

(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-C(O)-N(R20)-CH(R44)-(CH2)n-NH(R45), because both references teach the chemistry of -(R42)(R43)-[5-membered X heterocycle]-C(O)-NH- compounds, and further because Lin discloses the ATP binding site of AKT. Specifically, the co-crystal structure of compound 2aa in complex with PKA was determined by X-ray crystallography (pg 4163), and further teaches that PKA has previously been used as a surrogate for AKT in structure-based drug design. The co-crystal structure with PKA will guide the structure-based inhibitor design to develop more selective inhibitors for AKT (pg 4166 - pg 4167). Knowledge of the binding pocket of PKA, coupled with molecular modeling software, would have enabled one of ordinary skill in the art to have designed structural variations in order to have achieved a better binding fit and thus have optimized pharmaceutical activity.

Regarding claim 2, the combination of Duckworth and Lin discloses a compound of Formula (I) where R41 is a pyrazole such that Q is nitrogen, Y is -CR70, Z is -CR48, R30 is C1-6 alkyl, R70 is hydrogen or halogen and R48 is hydrogen or C1-6 alkyl (Duckworth - para [0003] -[0007]); R42 is hydrogen or C1-6 alkyl; R43 is hydrogen or C1-6 alkyl; and X is O or S (Duckworth - para [0003] -[0007]); R44 is -(CR60R61)m-AAR where R60 and R61 are hydrogen, m is 1 and -AAR is a substituted phenyl with two chloro groups [R44 is -CH2-phenyl(Cl)2]; R45 is H; R20 is H; and n is 1 (Lin - pg 4166).

Regarding claim 3, the combination of Duckworth and Lin discloses a compound of Formula (AA) where R1 is a pyrazole as shown such that R6 is C1-6 alkyl; and R7 is hydrogen or C1-6 alkyl (Duckworth - para [0003] -[0007]); R2 is hydrogen or C1-6 alkyl; R3 is hydrogen or C1-6 alkyl; and X is O or S (Duckworth - para [0003] -[0007]); R4 is -(CH2)m-aryl where the aryl is a substituted phenyl with two chloro groups and m is 1 [R4 is -CH2-phenyl(Cl)2]; R5 is hydrogen and n is 1 (Lin - pg 4166).

-- see supplemental box --

1093

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/53269

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
– Box No. V(2) – Citations and explanations:

Regarding claim 4, the combination of Duckworth and Lin discloses: N-[2-amino-1-(dichlorophenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; a compound of claim 1 where R41 is a pyrazole such that Q is nitrogen, Y is -CR70, Z is -CR48, R30 is C1 alkyl, R70 is hydrogen and R48 is hydrogen (Duckworth - para [0003] -[0007]); R42 is hydrogen, R43 is hydrogen, and X is O or S (Duckworth - para [0003] -[0007]); R20 is H; R44 is -CH2-phenyl(Cl)2; and R45 is H (Lin - pg 4166).
The combination of Duckworth and Lin does not expressly disclose N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide, where R44 is -CH2-phenyl [unsubstituted]. However, it would have been encompassed within the knowledge level of one of ordinary skill in the art to have utilized the moiety, HN(R20)-CH(R44)-(CH2)n-NH(R45), where R44 is -CH2-phenyl [unsubstituted], in the preparation of the compound of claim 1 based on the Lin's disclosure of the 3D structure of the binding pocket of PKA, coupled with molecular modeling software. Thus, it would have been obvious to one of ordinary skill in the art would have enabled one of ordinary skill in the art to have designed structural variations in order to have achieved a better binding fit and thus have optimized pharmaceutical activity.

Regarding claim 5, the combination of Duckworth and Lin discloses a pharmaceutical composition comprising a compound according to claim 1 (Duckworth - para [0003] -[0007]; Lin - pg 4166) and a pharmaceutically acceptable carrier (Duckworth - para [0032]).

Regarding claim 6, the combination of Duckworth and Lin discloses a process for preparing a pharmaceutical composition containing a pharmaceutically acceptable carrier and an effective amount of a compound of formula (I), which process comprises bringing the compound of formula (I) into association with a pharmaceutically acceptable carrier (Duckworth - para [0033] - para [0038]).

Regarding claim 37, the combination of Duckworth and Lin discloses a compound of formula (I) where R41 is ethyl or methyl; R42 is a pyrazole such that Q is nitrogen, Y is -CH-, Z is -CR48, R30 is methyl or ethyl, where R48 is hydrogen or methyl; R43 is hydrogen; and X is O or S (Duckworth - para [0033] - para [0038]); R44 is -CH2-phenyl where the phenyl is substituted by two chloro substituents; R45 is hydrogen; R20 is hydrogen; and n is 1 (Lin - pg 4166).
The combination of Duckworth and Lin does not expressly disclose where R44 is -CH2-phenyl where the phenyl is substituted by two fluoro substituents. However, taking in consideration Lin's dislosure of the 3D structure of the binding pocket of PKA and availability of molecular modeling software, it would have been encompassed within the knowledge level of one of ordinary skill in the art to have utilized the moiety, HN(R20)-CH(R44)-(CH2)n-NH(R45), where R44 is -CH2-phenyl(F)2 [difluoro-substituted], in the preparation of the compound of formula (I), with the aim of achieving structural variations with a better binding fit thereby optimizing their pharmaceutical activity.

Regarding claim 40, see the discussion set forth above for claims 3-4. The combination of Duckworth, Lin and Thompson discloses: N-[2-amino-1-(phenylmethyl)ethyl]-5-(1-methyl-1H-pyrazol-5-yl)-2-thiophenecarboxamide; where R41 is a pyrazole such that Q is nitrogen, Y is -CR70, Z is -CR48, R30 is C1 alkyl, R70 is hydrogen and R48 is hydrogen (Duckworth - para [0003] -[0007]); R42 is hydrogen, R43 is hydrogen, and X is O or S (Duckworth - para [0003] -[0007]); R20 is H; R44 is -CH2-phenyl; and R45 is H (Lin - pg 4166).

Regarding claims 41-42, see the discussion set forth above for claims 1 and 4. The combination of Duckworth and Lin discloses: N-{(1S)-2-amino-1-[(2',4'-dichlorophenyl) methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophene- carboxamide, a compound where R42 is a pyrazole such that Q is nitrogen, Y is -CR70, Z is -CR48, R30 is methyl, R70 is chloro and R48 is hydrogen (Duckworth - para [0003] - para [0007]); R41 is methyl, R43 is hydrogen, and X is S (Duckworth - para [0003] - para [0007]); R20 is H; R44 is -CH2-phenyl(Cl)2; and R45 is H (Lin - pg 4166). The combination of Duckworth and Lin does not expressly disclose N-{(1S)-2-amino-1-[(3-fluorophenyl)methyl]ethyl}-4-(4-chloro-1-methyl-1H-pyrazol-5-yl)-5-methyl-2-thiophenecarboxamide, where R44 is -CH2-phenyl(F). It would have been encompassed within the knowledge level of one of ordinary skill in the art to have utilized the moiety, HN(R20)-CH(R44)-(CH2)n-NH(R45), where R44 is -CH2-phenyl(F), in the preparation of the compound of claim 1; in order to practice the claim as described without undue experimentation. Knowledge of the binding pocket of PKA, coupled with molecular modeling software, would have enabled one of ordinary skill in the art to have designed structural variations in order to have achieved a better binding fit and thus have optimized pharmaceutical activity.

Claims 7-36 and 38-39 lack an inventive step under PCT Article 33(3) as being obvious over Duckworth in view of Lin, as above, and further in view of WO 2006/136837 A2 to Thompson et al. (hereinafter "Thompson").

Regarding claim 7, the combination of Duckworth and Lin does not expressly disclose a method of treating cancer, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of a compound of formula (I). Thompson discloses a method of treating a disease (pg 1, ln 5-10; pg 11, ln 5-9) mediated by PKB and PKA, such as cancer or arthritis (pg 118, ln 15 - pg 119, ln 36), in a mammal in a mammal in need thereof (pg 9, ln 15-19), which comprises administering to such mammal a combination of an ancillary compound and a therapeutically effective amount of a pyrazole-containing heteroaryl (thiophene)-alkylamine compound of the formula:
(R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-CO2H,
wherein R30 is hydrogen, R48 is hydrogen and R70 is C1-5 alkyl; R42 is -CH(phenyl)(N(CH3)2) and R43 is hydrogen; and X is S (pg 5, ln 15 - pg 6, ln 30; pg 16, ln 5-37; pg 18, ln 34-37). It would have been obvious to one of ordinary skill in the art to add the teachings of Thompson concerning a method of treating a disease, such as cancer or arthritis, which comprises administering to a mammal a composition comprising a therapeutically effective amount of a pyrazole-containing thiophene carboxylic acid compound to the teachings of the combination of Duckworth and Lin concerning a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula (I) as the technology is so similar (i.e., the combination of Duckworth and Lin, as well as Thompson, teach the pharmacophore: (R30)(R48)(R70)-pyrazole-(R42)(R43)-[5-membered X heterocycle]-C(O)-); in order to practice the claim as described without undue experimentation. Knowledge of the binding pocket of PKA, coupled with molecular modeling software, would have enabled one of ordinary skill in the art to have designed structural variations of the PKA/PKB inhibitors in order to have achieved a better binding fit and thus have optimized pharmaceutical activity.

-- see supplemental box --

1094

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/53269

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
– Box No. V(3) – Citations and explanations:

Regarding claim 8, Thompson further discloses where the mammal is a human (pg 14, ln 10-13).

Regarding claim 9, see the discussion set forth above for claims 3 and 7. The combination of Duckworth, Lin and Thompson discloses a method of treating a disease (Thompson - pg 1, ln 5-10; pg 11, ln 5-9), such as cancer or arthritis (Thompson - pg 118, ln 15 - pg 119, ln 36), in a mammal in a mammal in need thereof (Thompson - pg 9, ln 15-19), which comprises administering to such mammal a combination of an ancillary compound and a therapeutically effective amount (Thompson - pg 1, ln 5-10) of a compound of formula (AA) (Duckworth - para [0003] -[0007]; Lin - pg 4166).

Regarding claim 10, it is obvious for reasons set forth above for claims 8 and 9.

Regarding claim 11, Thompson discloses where the cancer is glioma, breast, colon, kidney, lung, liver, ovarian, pancreatic and prostate (pg 118, ln 15 - pg 119, ln 36).

Regarding claim 12, it is obvious for reasons set forth above for claims 9 and 11.

Regarding claim 13, see the discussion set forth above for claims 1 and 7. The combination of Duckworth, Lin and Thompson discloses the use of a compound of formula (I) (Duckworth - para [0003] -[0007]; Lin - pg 4166) in the manufacture of a medicament for use in treating a disease such as cancer or arthritis (Thompson - pg 9, ln 7-10).

Regarding claim 14, see the discussion set forth above for claims 1 and 7. The combination of Duckworth, Lin and Thompson discloses a method of inhibiting Akt (PKB) activity in a mammal in need thereof (Thompson - pg 9, ln 20-23), which comprises administering to such mammal a therapeutically effective amount of a compound of formula (I) (Duckworth - para [0003] - [0007]; Lin - pg 4166).

Regarding claim 15, it is obvious for reasons set forth above for claims 8 and 14.

Regarding claim 16, see the discussion set forth above for claims 1 and 7. The combination of Duckworth, Lin and Thompson discloses a method of treating cancer, in a mammal in need thereof, which comprises administering to such mammal a therapeutically effective amount of (Thompson - pg 1, ln 5-10; pg 9, ln 15-19; pg 11, ln 5-9; pg 118, ln 15 - pg 119, ln 36) a) a compound of formula (I) (Duckworth - para [0003] -[0007]; Lin - pg 4166); and b) at least on anti-neoplastic agent ('an ancillary compound' Thompson - pg 76, ln 31 - pg 77, ln 36; pg 83, ln 39 - pg 86, ln 14; pg 88, ln 21 - pg 89, ln 42).

Regarding claim 17, Thompson discloses where the at least one anti-neoplastic agent is an anti-microtubule agent or a platinum coordination complex (pg 76, ln 31 - pg 77, ln 36; pg 83, ln 39 - pg 85, ln 5; pg 88, ln 21 - pg 89, ln 42).

Regarding claim 18, Thompson discloses where the at least one anti-neoplastic agent is an anti-microtubule agent such as a diterpenoid or vinca alkaloid (pg 76, ln 31 - pg 77, ln 36; pg 83, ln 39 - pg 85, ln 5).

Regarding claim 19, Thompson discloses where the at least one anti-neoplastic agent is a diterpenoid [retinoid] (pg 76, ln 31 - pg 77, ln 36).

Regarding claims 20 and 25, Thompson discloses where the at least one anti-neoplastic agent is a vinca alkaloid such as vinorelbine (pg 83, ln 39 - pg 85, ln 5).

Regarding claims 21 and 24, Thompson discloses where the at least one anti-neoplastic agent is a platinum coordination complex such as carboplatin (pg 88, ln 21 - pg 89, ln 42).

Regarding claims 22 and 23, Thompson discloses where the at least one anti-neoplastic agent is paclitaxel (pg 85, ln 6 - pg 86, ln 14).

Regarding claims 26 and 27, Thompson discloses where the at least one anti-neoplastic agent is a signal transduction pathway inhibitor such as VEGF or PDGF (pg 95, ln 8 - pg 98, ln 39). The particular species of VEGF or PDGF would have been encompassed within the knowledge level of one of ordinary skill in the art.

Regarding claim 28, Thompson discloses where a signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase such as Raf (pg 95, ln 8 - pg 98, ln 39). The particular species of Raf would have been encompassed within the knowledge level of one of ordinary skill in the art.

Regarding claims 29-30, the combination of Duckworth, Lin and Thompson does not expressly disclose where a signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase selected from the src family of kinases or a particular species thereof. The particular family of serine/threonine kinases as signal transduction pathway inhibitors and particular species thereof would have been encompassed within the knowledge level of one of ordinary skill in the art, given the lack of unexpected results.

Regarding claim 31, the combination of Duckworth, Lin and Thompson does not expressly disclose where the signal transduction pathway inhibitor is an inhibitor of Ras oncogene or a particular species thereof. The particular family of signal transduction pathway inhibitors and particular species thereof would have been encompassed within the knowledge level of one of ordinary skill in the art, given the lack of unexpected results.

Regarding claim 32, Thompson discloses where a signal transduction pathway inhibitor is an inhibitor of a serine/threonine kinase such as PI3K (pg 98, ln 41 - pg 99, ln 35).

– see supplemental box –

1095

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US 08/53269

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**
Continuation of:
-- Box No. V(2) – Citations and explanations:

Regarding claims 33-34, Thompson discloses where the at least one anti-neoplastic agent is a cell cycle signaling inhibitor such as CDK4 (pg 103, ln 11 - pg 105, ln 9).

Regarding claim 35, it is obvious for reasons set forth for claims 7 and 16.
Regarding claim 36, it is obvious for reasons set forth above for claims 13 and 16.
Regarding claim 38, it is obvious for reasons set forth above for claims 7 and 11.
Regarding claim 39, it is obvious for reasons set forth above for claims 8 and 38.

Claims 1-42 have industrial applicability as defined by PCT Article 33(4) because the subject matter can be made or used in industry.

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE
PCT

PATENTE DE INVENCIÓN [X] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [X]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [X]
- Descripción de la invención [X]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [X]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-082387- -00000-0000
Fecha: 2009-08-06 17:19:24 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 1095

Carrera 13 No. 27-00 Piso 5,7y10
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SMITHKLINE BEECHAM CORPORATION

REFERENCIA	Radicación No.	9 82387
	Solicitud internacional	PCT/US2008/053269
	Fecha inicio fase nacional	07/09/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	10891

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 25 SET. 2009
adpall

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
SMITHKLINE BEECHAM CORPORATION

REFERENCIA	Radicación No.	9 82387
	Solicitud internacional	PCT/US2008/053269
	Fecha inicio fase nacional	07/09/2009
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	11809

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de quince reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 25 SET. 2009
adpa11